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Molecular epidemiology of prostate cancer: hormone-related genetic loci

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1. ABSTRACT

Prostate cancer is the most common non-skin cancer and the second leading cause of cancer deaths among men in most Western countries. Despite its high morbidity and mortality, the etiology of prostate cancer remains obscure. Although compelling laboratory data suggest a role for androgens in prostate carcinogenesis, most epidemiologic data, including serological and genetic studies, are inconclusive. In this chapter, we review the status of serologic studies and discuss the importance of intra-prostatic hormone levels in possibly clarifying the often-contradictory data on serologic studies. To provide insights and directions for epidemiologic research on hormones and prostate cancer, this review centers on the molecular epidemiology of hormone-related genetic loci. These loci have been investigated in a number of studies to date and will undoubtedly expand even further as rich new genetic information sources and high-throughput genotyping and analysis methods become

available. Due to the enormous number of these loci, we recommend careful analysis and cautious interpretation of studies of genetic markers, including microsatellites and single nucleotide polymorphisms (SNPs), as false positive and negative results are likely due to limited statistical power, multiple hypothesis testing, population stratification, or non-representative population sampling. This review also highlights the need for replication in various populations, as well as reasons for performing functional analyses of SNPs, a critical and often under-appreciated component of molecular epidemiologic investigations. The time is ripe for concerted, large-scale multidisciplinary investigations that incorporate molecular genetics, biochemistry, histopathology, and endocrinology into traditional epidemiologic studies. Such collaboration will lead to a deeper understanding of the etiologic pathways of prostate cancer, ultimately yielding better preventive, diagnostic, and therapeutic strategies.

2. INTRODUCTION

Prostate cancer is the most common non-skin cancer among American men, with 234,460 new cases expected in 2006, and it ranks third in number of estimated male cancer deaths (n=27,350), behind only lung and colorectal cancer (1). Despite the magnitude of prostate cancer incidence and mortality, few risk factors have been identified other than age, race, and family history.

Prostate cancer is a hormone-mediated cancer. Abundant biological data have shown that the growth and maintenance of the prostate are dependent on androgens, that prostate cancer regresses after androgen ablation or anti-androgen therapy, and that administration of testosterone induces prostate tumors in laboratory animals (2-4). Estrogen compounds have long been used to control prostate cancer growth, though recognition of their serious cardiac and sexual side effects have diminished their use (5). Similarly, strong laboratory evidence shows that vitamin D, another steroid hormone, has strong anti-proliferative and pro-apoptotic effects on prostate cancer (6). In addition, obesity, which has been linked to elevated risk of aggressive prostate cancer and prostate cancer death (7), is associated with lower levels of sex hormone-binding globulin (SHBG) and presumably higher levels of free testosterone (8). However, despite numerous studies of both prospective and retrospective designs, there has been no convincing epidemiological evidence linking circulating levels of these hormones to prostate cancer risk (6, 9). A number of methodological issues, discussed below, have been suggested to explain these inconsistencies.

Family history is an established risk factor for prostate cancer: men with a first-degree affected relative (father, brother) have a 2-3-fold increased risk (10), and it has been estimated that 42% (95% CI 29-50%) of prostate cancer risk is explained by genetic factors, the highest for any human cancer (11). More recent epidemiological investigations have attempted to exploit this known heritability by focusing on hormone-related genes as a path to understanding the role of hormones in prostate cancer. However, though these studies provide exciting new evidence and leads regarding the specific roles played by hormones and hormone-related genetic loci, results to date have not been conclusive. Indeed, despite the large number of publications resulting from the sudden wealth of genetic data enabled by recent genotyping technology advances, few of the reported findings have been replicated (12), and this trend is likely to continue as the technologies improve further. It is possible that the familial and sporadic forms of the disease are etiologically distinct.

This review summarizes current perspectives on steroid hormone metabolism, epidemiologic data on androgenic and non-androgenic hormones in prostate cancer, and polymorphisms of genes involved in androgen metabolism and regulation. Through this effort, we attempt to provide insights and directions for future research on hormone-related genetic loci and prostate cancer.

3. ANDROGENS

3.1. Biosynthesis and Metabolism of Androgens

Androgens are steroid hormones that induce the differentiation and maturation of the male reproductive organs and the development of male secondary sex characteristics. In men, androgens are formed primarily in the testes and the adrenal gland, and to a lesser extent in peripheral tissues, such as the prostate and skin. Formation of androgens in the endocrine glands occurs by well-characterized biosynthetic pathways (Figure 1).

Testosterone is the principal androgen in circulation, while dihydrotestosterone (DHT) is the primary nuclear androgen and the most potent androgen. In the circulation of adult males, roughly 44% of testosterone is bound with high affinity to SHBG, 54% is bound with low affinity to albumin, and only 1-2% of testosterone exists in a free (unbound) state. About 25% of the DHT in the circulation is secreted by the testes, while most (65-75%) arises from conversion of testosterone in peripheral tissue in a reaction catalyzed by the enzyme steroid 5 alpha-reductase or from circulating inactive androgens, such as androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEAS). In humans, two steroid 5 alpha-reductase isoenzymes have been identified. The type 1 enzyme (encoded by the *SRD5A1* gene) is expressed mostly in skin and hair, whereas the type 2 enzyme (encoded by the *SRD5A2* gene) is localized primarily in androgen target tissue, including genital skin and the prostate (13).

In men, the prostate is a major site of non-testicular DHT production from testosterone. Free testosterone in circulation enters prostate cells by passive diffusion, whereas albumin-bound testosterone, because of its low affinity for albumin, can disassociate from albumin, allowing it to enter prostatic cells. In addition, recent evidence of SHBG receptors on the surface of prostate cells suggests that SHBG-bound testosterone may also enter prostate cells (14, 15). Figure 2 shows the metabolic pathways of androgens within the prostate gland.

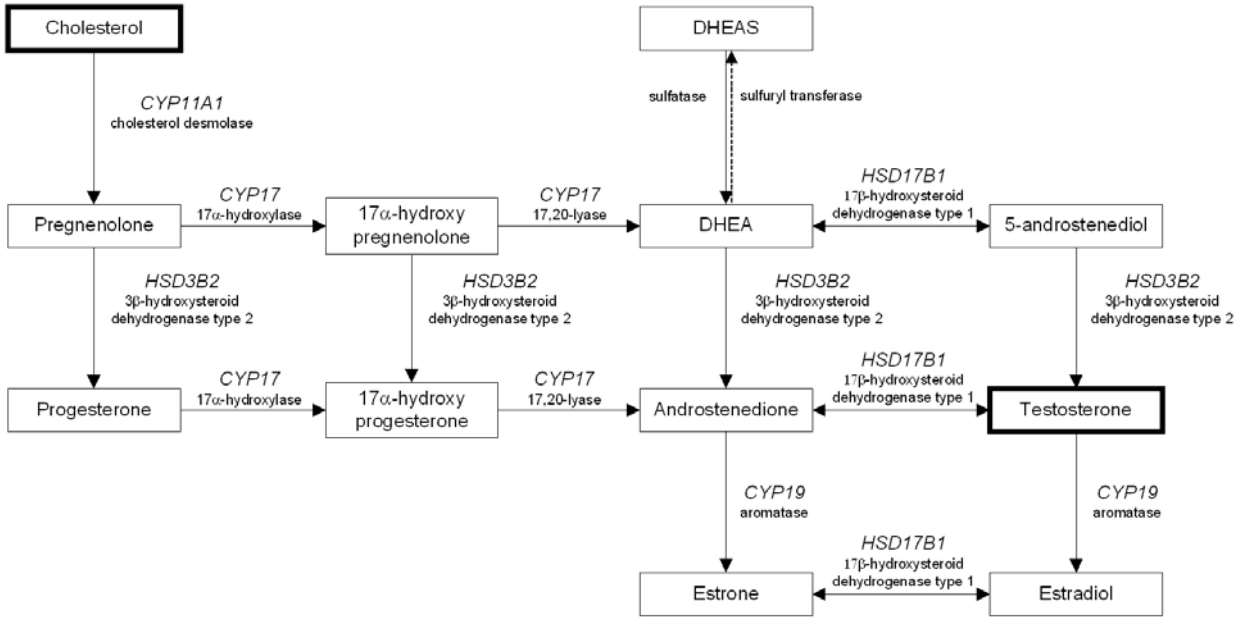

Figure 1. Androgen metabolism pathways in the endocrine system.

The concentration of DHT in serum is a fraction of that of testosterone (16), whereas the concentration of DHT in prostatic tissue is several times higher than that of testosterone, suggesting that DHT levels in tissue are important in prostate development and tumorigenesis. However, tissue levels of testosterone and DHT are difficult to measure in epidemiologic studies, and thus, the serum concentration of 3 alpha-diol G (3 alpha androstanediol glucuronide; AAG) is commonly used as an indirect measure of steroid 5alpha-reductase enzymatic activity or, more generally, of intra-prostatic androgenicity. The concentration of 3alpha-diol G in serum correlates well with steroid 5alpha-reductase activity in genital skin (17, 18). Although serum levels of 3alpha-diol G may reflect enzyme activities of both the type 1 and type 2 steroid 5alpha-reductase enzymes, recent data from studies of finasteride, a type 2 steroid 5alpha-reductase inhibitor, show that serum levels of DHT and 3alpha-diol G decrease concomitantly in treated men, suggesting that serum levels of 3alpha-diol G may predominantly reflect the activity of the type 2 steroid 5alpha-reductase (19).

3.2 Androgen Action on the Prostate

The action of DHT in the prostate is mediated by the androgen receptor (AR) (Figure 2). Within the prostate, DHT binds to the AR to form an intracellular complex which binds to androgen-response elements in the DNA of prostate cells, ultimately inducing proliferation. Though the tissue concentration of DHT necessary to initiate the androgen cascade is unknown, just a minute amount is required to trigger androgenic action in prostate cancer patients who have undergone androgen ablation treatment, perhaps because such patients have hypersensitive ARs (20, 21). In the absence of androgen, non-androgenic hormones including estradiol, vitamin D, and insulin-like growth factors (IGFs) can bind ARs, triggering androgenic action (22, 23). In addition, the activity of the AR is modulated by a series of coactivator proteins, including ARA54, ARA55, ARA70, ARA160, p160, BRCA1, AIB1, and CBP, which can enhance AR transcriptional activity several-fold (24-26). Thus, androgenic action within the prostate is determined not only by androgen concentration but also by numerous other factors, including factors yet to be identified. However, no epidemiologic studies have directly assessed tissue hormone levels or androgenic action within the prostate, due in part to the difficulty in collecting prostate tissue from control subjects in case-control studies, or from men at baseline in cohort studies.

3.3. Androgens and Prostate Cancer: Epidemiologic Evidence

Most epidemiologic studies have compared serum levels of androgens in prostate cancer cases with those in healthy subjects in either case-control or prospective studies. In case-control studies, blood samples from cancer patients are collected after diagnosis (usually before treatment) and assayed for hormone levels. Thus, the presence of disease may have an effect on circulating levels of hormone. Moreover, these types of cross-sectional studies make it difficult to establish a temporal relationship between androgens and prostate cancer. In contrast, prospective studies, such as nested case-control studies, compare serum levels of hormones in pre-diagnostic blood samples from incident cases identified in a prospective follow-up to those of healthy controls selected from the same cohort. Because blood samples of the case subjects are usually collected several years before the diagnosis of cancer, potential effects of disease on the measurement of hormones are presumably minimized.

Several prospective studies have evaluated the role of serum hormones in prostate cancer. Although two

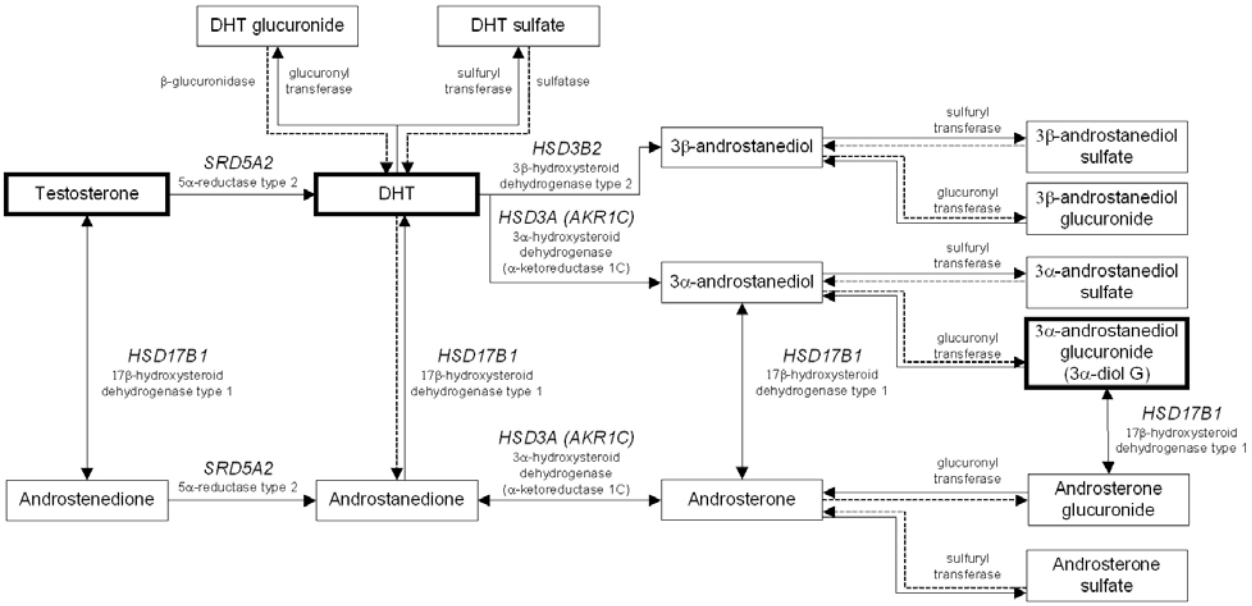

Figure 2. Androgen metabolism pathways within the prostate gland.

studies reported a statistically significant association between serum levels of testosterone and prostate cancer (16, 27), several found suggestive, but statistically non-significant, associations between prostate cancer and serum levels of testosterone and DHT (28, 29). Recent studies have shown elevated risk of low-grade prostate cancer and reduced risk of high-grade prostate cancer to be associated with higher levels of serum testosterone (30, 31). This might explain, in part, inconsistent results of studies linking obesity to both increased risk of aggressive prostate cancer and decreased risk of overall and low-grade tumors (7), as obesity is associated with lower serum levels of androgens (8). Earlier studies using the ratio of serum testosterone to DHT as an indirect measure of steroid 5alpha-reductase type 2 activity, suggested a role for the steroid 5alpha-reductase type 2 enzyme (28, 29). However, more recent studies have found no significant association between prostate cancer risk and serum levels of 3alpha-diol G, a surrogate marker for steroid 5alpha-reductase activity within the prostate (16, 31-37).

In most of these studies, the failure to show an association between androgen levels and prostate cancer risk may be due, in part, to methodologic limitations that include difficulty in making reliable measurements of circulating hormone levels in an epidemiologic setting. It is possible that free, unbound testosterone is more etiologically relevant than total testosterone, but because it is infeasible to directly measure free testosterone in epidemiological studies, its concentration is often estimated indirectly from measures of total testosterone and SHBG. Moreover, the statistical power of some studies is often limited by small sample size, by the observation of relatively small differences (usually 10-15%) between cases and controls, or by fairly large intra- and inter-assay laboratory variations in circulating hormone assays (38). In addition, it is unclear whether circulating levels of androgens reflect the androgenic environment within the prostate, since DHT in the prostate gland mainly comes from intra-prostatic conversion of testosterone. Also unclear is whether cumulative exposure to androgens over a lifetime or exposure at certain points in life is more relevant in prostate carcinogenesis. Hormonal changes during the prenatal and peri-pubertal period may be of etiologic importance, because prostate development, including substantial epithelial cell differentiation, occurs at these critical time periods (39). Accordingly, if early exposure to androgens is most critical for the development of prostate cancer, then most epidemiologic studies that measure circulating hormone levels of hormones in study subjects who are typically in their sixth decade of life would miss the etiologically relevant period of exposure. Thus very long-term studies may be needed to examine this hypothesis. Lastly, the heterogeneity of prostate cancer may influence results, as evidenced by the different findings observed for serum testosterone by tumor aggressiveness (30). Future studies will need to address this by stratifying by disease grade and/or stage.

A better understanding of the hormonal milieu within the prostate gland and its relationship to circulating hormones would be critical to interpret results from serum-based studies. However, epidemiologic studies of tissue androgen levels are impeded by various methodologic problems associated with prostate tissue collection and methods for tissue hormone measurements. These problems are compounded by the lack of a normal comparison group for analytic studies, since ethical considerations often preclude the collection of "normal" tissue from healthy subjects. In addition, the high prevalence of latent prostate tumors in elderly men means that identification of age-matched controls with no histological evidence of prostate cancer is very difficult.

3.4. Androgen-Related Genes

Because prostate cancer is an androgen-mediated tumor, it is likely that markers in genes whose products are involved in androgen biosynthesis and metabolism are involved in prostate cancer etiology. Ross et al. (40) first proposed a polygenic model to help explain the racial/ethnic difference in prostate cancer risk. That model triggered a series of studies that investigated the involvement of genes encoding cytochrome P450 17alpha-hydroxylase (*CYP17*), aromatase (*CYP19*), steroid 5alpha-reductase (*SRD5A2)*, 3beta-hydroxysteroid dehydrogenase (*HSD3B2*), and androgen receptor (*AR*) in prostate cancer. These candidate genes and several others are discussed in this review, and are summarized in Table 1. Although these data are promising and accumulating at a remarkable pace, they are still too sparse to support a definitive role for any particular gene.

3.4.1. AR and AR Coactivators

Possibly the most-studied gene with regard to prostate cancer is that encoding the AR. The AR is expressed in all histological types and stages of prostate cancer (41). Numerous somatic mutations in the *AR* gene, located on the long arm of the X chromosome, have been reported among prostate cancer patients enrolled in clinical studies. Most of these mutations have been detected in tumor tissue of late stage prostate carcinoma, with consistent findings showing that somatic mutation of the *AR* gene is involved in the progression and aggressiveness of prostate cancer (41). Most epidemiologic studies of the *AR* gene have focused on two trinucleotide repeat polymorphisms in exon 1, the $(CAG)_n$ and $(GGN)_n$ where N stands for any nucleotide) repeats, which encode polyglutamine and polyglycine, respectively. The $(CAG)_n$ repeat length ranges from 11 to 31 repeats in most men, and experimental data show that shorter $(CAG)_n$ repeat lengths are linked to increased AR trans-activation activity (42, 43). In addition, $(CAG)_n$ repeat length has been linked to male pattern baldness (44, 45), a clinical condition associated with higher DHT levels and prostate cancer risk. Epidemiologic studies show, that in general, shorter $(CAG)_n$ repeat lengths are associated with increased risk in many but not all populations (46-73). Evidence of association for the second repeat, $(GGN)_n$, is less consistent than that for $(CAG)_n$, and the story is complicated by variations in the way in which the numbers of repeats were counted in the various studies: some counted only $(GGC)_n$, while others counted any $(GGN)_n$. However, a recent meta-analysis reports that *AR* $(CAG)_n$ or $(GGN)_n$ repeat length is unlikely to have a major biological role in prostate cancer because the pooled effect size is not large, and the absolute difference in number of $(CAG)_n$ or $(GGN)_n$ repeats between cases and controls is less than one (74). It is interesting to note, however, that on average, $(CAG)_n$ repeat lengths correspond to observed racial variations in prostate cancer risk, such that African Americans, who have a high risk of prostate cancer, have a shorter $(CAG)_n$ repeat length, Caucasians have an intermediate repeat length, and Asian men, who are at much lower risk of prostate cancer have a longer repeat length.

Two other polymorphisms in the *AR* gene have been investigated for their associations with prostate cancer. The first is the R726L mutation in the hormone binding region of exon E, which despite a reported 6-fold increase in risk, has been observed only in Finnish men (75, 76). This marker is in strong linkage disequilibrium (LD) with the (CAG)n repeat marker, such that those with the variant allele invariably have 26 (CAG)n repeats. The second polymorphism is StuI, also designated E211G/A, which is a synonymous polymorphism located on exon 1 between the (CAG)n and (GGN)n repeats and is in linkage disequilibrium with both. This marker has been linked to prostate cancer risk in African-Americans and in Brazilians (40, 77), but not Australians (71). The observed associations of the R726L and the StuI markers with prostate cancer are likely to be influenced by their linkage with the trinucleotide repeats, and the synonymous nature of the StuI marker strongly suggests that this marker's association is unlikely to be causal.

AR coactivators enhance transactivation of the AR several fold (24) and therefore potentially increase the risk of prostate cancer. One AR co-activator, encoded by the *AIB1* (Amplified in Breast Cancer 1) gene located in chromosome band Xq11-12, has a (CAG)n/(CAA)n (polyglutamine) trinucleotide repeat. Two epidemiologic studies have investigated the role of this repeat polymorphism in prostate cancer: one found a positive association between *AIB1* (CAG)n repeat length and prostate cancer (78), and the other reported no association (79). Because of their importance in modulating the effects of androgenic action, future studies should be directed at clarifying the combined effects of AR and AR coactivators in prostate cancer risk.

3.4.2. CYP17

Cytochrome P450c17alpha hydroxylase, encoded by the *CYP17* gene located in chromosome band 10q24.3, catalyzes critical steps in the biosynthesis of testosterone. A single base pair change (T to C) in the 5'-untranslated region (UTR) of the *CYP17* gene (C nucleotide, or A2 allele), has been linked to male pattern baldness (80), a putative risk factor for prostate cancer. Interestingly, the A2 allele of this *CYP17* marker is also associated with higher levels of serum estrone and an increased risk of breast cancer compared to the A1 allele (81). However, the relationship between *CYP17* and prostate cancer is inconclusive. Of the 16 epidemiologic studies that have examined the role of *CYP17* in prostate cancer (57, 65, 68, 70, 82-93), 4 found a positive association with the A2 allele (82, 84, 87, 88), while 4 others found elevated risk associated with the A1 allele (83, 85, 91, 93). Nevertheless, a recent meta-analysis concluded that evidence to date provides no evidence of overall association of the *CYP17* gene with prostate cancer (94). In addition, two epidemiologic studies with data on circulating levels of hormones found no association between the *CYP17* marker and serum levels of either testosterone or 3alpha-diol G (86, 95). These results suggest that the effect of *CYP17* on prostate cancer, if any, is likely to be small.

Table 1. Epidemiologic studies of hormone metabolizing genetic loci and prostate cancer

Gene (locus) *Product*	Variant	Design	Country/ Population	Cases/ Controls	Results (OR and 95% CI)	Reference
AR (Xq11-12) *Androgen receptor*	$(CAG)_n$	Case-control	U.S., White	57/169	≥20: 1.00 <20: 2.10 (1.11-3.99)	46
		Case-control	U.S., White	301/277	≥22: 1.00 <22: 1.23 (0.88-1.73)	48
		Nested case-control	U.S., White	587/588	≥26: 1.00 ≤18: 1.52 (0.92-2.49)	47
		Case-control	France and Germany, White	132/105	≥22: 1.0 <22: 1.2 (0.7-2.0)	50
		Case-control	U.K., White	178/195	≤21: 1.00 >21: 1.00 (0.96-1.03)	51
		Case-control	Sweden and Japan	59/36 Swedes 34/33 Japanese	Significantly increased risk with shorter repeats	52
		Case-control	Sweden	190/186	No association with risk; shorter repeats associated with younger age at diagnosis and higher stage and grade	211
		Case-control	U.S., White	270/ (controls from another study)	≤ 21: 1.0 >21: 0.85 (0.53-1.35)	53
		Case-control	China	189/301	≥23: 1.0 <23: 1.65 (1.14-2.39)	54
		Case-control	Australia	448/456	Every 5 CAG repeats: 0.98 (0.84-1.15)	56
		Case-control	France	268/156	>24: 1.0 ≤20: 1.1 (0.60-2.02)	57
		Case-control	U.S., White	449/558	≥23: 1.0 <23: 1.75 (1.05-2.94)	58
		Case-control	Finland	461/574	>18: 1.00 ≤18: 1.47 (1.00-2.16)	59
		Case-control	U.S., Hispanic	82/145	>18: 1.00 ≤18: 2.7 (1.21-6.01)	60
		Case-control	U.S., 84% White	245/222	≥22: 1.00 <22: 0.82 (0.55-1.22)	61
		Nested case-control	U.S., 94% White	300/300	≥22: 1.00 <22: 0.89 (0.65-1.23)	62
		Case-control (BPH controls)	Austria	190/190	6-20: 1.00 21-22: 1.28 (0.76-2.15) 23-32: 1.07 (0.67-1.73)	63
		Case-control	Taiwan	66/104	≥23: 1.00 <23: 0.45 (0.29-1.05)	64
		Case-control	Canada	483/548	>18: 1.00 ≤ 18: 1.07 (0.7-1.6)	65
		Case-control	Brazil, mixed	133/279	>21: 1.00 ≤21: 1.23 (0.6-2.3)	66
		Case-control	Scotland	100/144	≥22: 1.00 <22: Non-significant, ORs not reported, chisq p=0.21	67
		Family-based case-control	U.S., 91% White	440/480	≥22: 1.00 <22: 0.90 (0.61-1.32)	68
		Case-control	U.S., Black	118/567	Each CAG repeat: OR=1.05 (0.98-1.13)	69
		Case-control	U.K., mixed	267/795	>22: 1.00 ≤22: 0.68 (0.50-0.91)	70
		Case-control	U.S., mostly White	591/538	≥22: 1.00 <22: 1.1 (0.9-1.4)	72
		Case-control	India	113/133	>22: 1.00 ≤22: 2.96 (1.68-5.21)	73
		Case-control	India	87/120	>19: 1.00 ≤19: 7.01 (3.52-13.94)	212
	$(GGN)_n$	Case-control	U.S., White	301/277	≥16: 1.0 <16: 1.60 (1.07-2.41)	48
		Nested case-control	U.S., White	582/794	Not 23: 1.0 23: 1.20 (0.97-1.49)	49
		Case-control	U.K., White	178/195	≤16: 1.0 >16: 1.06 (0.57-1.96)	51
		Case-control	China	189/301	≥23: 1.0 <23: 1.12 (0.71-1.78)	54
		Case-control	U.S., 84% White	245/222	≥17: 1.00 <17: 1.51 (0.99-2.32)	61
		Nested case-control	U.S., 94% White	300/300	>17: 1.00 ≤17: 0.80 (0.57-1.12)	62
		Case-control	Scotland	100/144	≥17: 1.00 <17: ORs not reported, chisq p=0.75	67
		Family-based case-control	U.S., 91% White	440/480	>16: 1.00 ≤16: 1.04 (0.71-1.52)	68
		Case-control	U.K., mixed	267/795	>16: 1.00 ≤16: 1.06 (0.78-1.44)	70
		Case-control	U.S., mostly White	591/538	>16: 1.00 ≤16: 1.0 (0.9-1.4)	72

	R726L	Case-control	Finland	418/778	R: L:	1.00 5.8 (1.5-22.1)	76
	StuI, E211G/A	Case-control	Australia	815/719	G: A:	1.00 1.05 (0.79-1.39)	71
SRD5A2 (2p23) *Type II steroid 5 alpha reductase*	V89L (rs523349)	Nested case-control	U.S., White	584/799	VV: VL: LL:	1.00 0.96 (0.76-1.20) 0.84 (0.57-1.24)	103
		Case-control	U.S., mostly White	108/167	VV: VL, LL:	1.00 1.4 (0.8-2.2)	82
		Case-control	Italy	108/121	LL: VL,VV:	1.00 0.35 (0.09-1.32)	105
		Case-control	Japan	92/203	VV: VL: LL:	1.00 1.13 (0.61-2.08) 1.37 (0.70-2.71)	87
		Case-control	France	268/156	VV: VL: LL:	1.00 1.23 (0.80-1.88) 2.30 (0.98-5.40)	57
		Case-control	China	186/303	VV: VL: LL:	1.00 0.98 (0.60-1.58) 0.88 (0.53-1.47)	108
		Case-control	Canada	318/320	LL: VL: VV:	1.00 2.31 (0.97-5.48) 2.76 (1.17-6.50)	106
		Nested case-control	U.S., mixed	921/1295	VV: VL: LL:	1.00 0.95 (0.79-1.15) 1.15 (0.85-1.54)	109
		Case-control	Sweden	175/159	LL: VL: VV:	1.00 1.28 (0.62-2.63) 1.42 (0.70-2.89)	110
		Nested case-control	U.S., mixed	300/300	VV: VL: LL:	1.00 1.06(0.75-1.49) 0.99 (0.57-1.73)	111
		Case-control	U.S., 84% White	245/222	LL: VL,VV:	1.00 1.01 (0.56-2.25)	112
		Case-control	Japan	302/243	LL: VL,VV:	1.00 1.69 (1.07-2.65)	113
		Case-control	Canada	483/548	VV: VL: LL:	1.00 0.86 (0.6-1.3) 0.97 (0.6-1.6)	65
		Family-based case-control	U.S., 91% White	440/480	VV: VL,LL:	1.00 1.56 (1.08-2.25)	68
		Case-control	U.K., mixed	267/795	VV: VL: LL:	1.00 1.01 (0.74-1.38) 1.84 (1.15-2.98)	70
	R227Q	Case-control	China	176/268	RR: RQ:	1.00 2.85 (0.25-32.1)	108
	A49T (145G/A)	Nested case-control	U.S., Black and Hispanic	388/461	Blacks: AA: AT,TT: Hispanics: AA: AT,TT:	 1.00 3.28 (1.09-11.87) 1.00 2.50 (0.90-7.40)	104
		Case-control	Italy	108/121	AA: AT:	1.00 7.7 (0.39-150.5)	105
		Case-control	France	268/156	AA: AT:	1.00 0.8 (0.26-2.42)	57
		Case-control	China	170/256	No T alleles observed		108
		Case-control	Finland	449/588	AA: AT,TT:	1.00 1.04 (0.62-1.76)	107
		Case-control	Sweden	175/159	AA: AT,TT:	1.00 1.29 (0.40-4.15)	110
		Nested case-control	U.S., mixed	300/300	AA: AT,TT:	1.00 1.11 (0.58-2.11)	111
		Case-control	U.S., 84% White	245/222	AA: AT,TT:	1.00 0.63 (0.27-1.48)	112
		Family-based case-control	U.S., mostly White	440/480	AA: AT,TT:	1.00 0.84 (0.38-1.85)	213
		Family-based case-control	U.S., 91% White	440/480	AA: AT,TT:	1.00 0.84 (0.38-1.85)	68
		Case-control	U.K., mixed	267/795	AA: AT,TT:	1.00 0.93 (0.50-1.74)	70
	$(TA)_n$	Nested case-control	U.S., White	590/802	0/0: Non-0/Non-0:	1.00 0.47 (0.20-1.12)	102
		Case-control	France	268/156	0/0: 0/9: 9/9:	1.00 0.96 (0.58-1.56) 0.50 (0.11-2.26)	57

		Case-control	China	191/304	0/0: 1.00 0/9: 0.67 (0.39-1.12) 9/9: 0.74 (0.07-8.34)	108
		Case-control	Italy	108/121	0/0: 1.00 0/8,9/9: 0.95 (0.51-1.72)	105
		Nested case-control	U.S., mixed	300/300	0/0: 1.00 Non-0/Non-0: 0.68 (0.21-2.19)	111
		Case-control	U.K., mixed	267/795	0/0: 1.00 9/9,9/0: 1.11 (0.77-1.60)	70
AIB1 (Xq11-12) *Amplified in breast cancer 1*	$(CAG/CAA)_n$	Nested case-control	U.S., White	581/786	28/29: 1.00 29/29: 1.03 (0.77-1.37) 28/28: 1.10 (0.79-1.53)	79
		Case-control	China	189/299	29/29: 1.00 29/30,31,32: 1.58 (0.62-4.01) 29/28: 1.30 (0.83-2.03) 28/28: 2.12 (1.09-4.12)	78
CYP17 (10q24.3) *Cytochrome P450c17 alpha hydrolase*	5'UTR, MspA1 (rs743572)	Case-control	U.S., mostly White	108/167	A1/A1: 1.00 A1/A2,A2/A2: 1.7 (1.0-3.0)	82
		Case-control	Sweden	178/160	A2/A2: 1.00 A1/A2,A1/A1: 1.6 (1.0-2.5)	83
		Case-control	Austria	63/126	A1/A1: 1.00 A1/A2,A2/A2: 2.8 (1.0-7.8)	84
		Case-control	Japan	252/131	A2/A2: 1.00 A1/A2,A1/A1: 2.6 (1.4-4.8)	85
		Nested case-control	U.S., White	590/782	A1/A1: 1.00 A1/A2: 1.26 (0.99-1.59) A2/A2: 1.17 (0.85-1.61)	86
		Case-control	Japan	101/200	A1/A1: 1.00 A1/A2: 2.06 (1.06-4.00) A2/A2: 2.39 (1.04-5.46)	87
		Case-control	U.S., White	225/283	A1/A1: 1.00 A1/A2: 1.04 (0.57-1.91) A2/A2: 1.14 (0.77-1.70)	89
		Case-control	U.S., Black	71/111	A1/A1: 1.0 A1/A2: 2.0 (1.0-3.9) A2/A2: 2.8 (1.0-7.4)	88
		Case-control	France	268/156	A1/A1: 1.00 A1/A2: 0.95 (0.60-1.51) A2/A2: 0.94 (0.50-1.76)	57
		Case-control	U.S., mostly White	590/538	A1/A1: 1.00 A1/A2: 0.81 (0.63-1.05) A2/A2: 0.87 (0.61-1.26)	90
		Case-control	China	174/274	A2/A2: 1.00 A1/A2: 1.41 (0.91-2.17) A1/A1: 1.42 (0.83-2.48)	91
		Case-control	Taiwan	93/121	No ORs reported, p=0.701	92
		Case-control	Canada	483/548	A1/A1: 1.00 A1/A2: 0.85 (0.6-1.1) A2/A2: 0.84 (0.6-1.3)	65
		Family-based case-control	U.S., 91% White	440/480	A1/A1: 1.00 A1/A2,A2/A2: 0.91 (0.65-1.29)	68
		Case-control	Italy	384/360	A2/A2: 1.00 A1/A2: 2.50 (1.56-4.01) A1/A1: 3.11 (1.92-5.05)	93
		Case-control	U.K., mixed	267/795	A1/A1: 1.00 A1/A2: 1.12 (0.81-1.55) A2/A2: 1.10 (0.67-1.81)	70
CYP3A4 (7q21.1) *Cytochrome P450, family 3, subfamily A, polypeptide 4*	-391A/G, CYP3A4*1B (rs2740574)	Case-control	Canada	483/548	No *1B allele: 1.00 One *1B allele: 1.03 (0.6-1.7) Two *1B alleles: 0.73 (0.3-1.7)	65
		Family-based case-control	U.S., mostly White	440/480	No *1B allele: 1.00 Any *1B allele: 0.76 (0.48-1.20)	122
		Case-control	U.S.	622/396	No *1B allele: 1.00 Any *1B allele: 0.81 (0.45-1.44)	123
		Case-control	U.S., Black and White	145/103 Blacks 177/145 Whites	Blacks: Associated with more aggressive, but not less aggressive, disease Whites: Not associated	121
CYP3A5 (7q21.1) *Cytochrome P450, family 3, subfamily A, polypeptide 5*	CYP3A5*1	Family-based case-control	U.S., mostly White	440/480	No *1 allele: 1.00 Any *1 allele: 0.73 (0.51-1.05)	122
		Case-control	U.S.	622/396	No *1 allele: 1.00 Any *1 allele: 1.03 (0.67-1.59)	123
	CYP3A5*3 (A6986G)	Case-control	Japan	260/212	GG: 1.00 AG: 0.75 (0.52-1.11) AA: 0.47 (0.20-1.08)	124
CYP19 (15q21.1) *Aromatase*	(TTTA)n	Case-control	France	226/156	167bp: 1.00 187bp: 1.41 (1.01-1.98)	57

		Case-control	Japan	99/116	>8/>8: 1.00 ≤8/≤8: 1.80 (1.04-3.11)	96
		Family-based case-control	U.S., mostly White	439/479	11/11: 1.00 11/other: 1.33 (0.80-2.22) other/other: 1.03 (0.58-1.83)	98
	R264C (rs700519)	Case-control	U.S., White	88/241	CC: 1.00 CT: 1.72 (0.72-4.08)	58
		Case-control	Japan	147/266	No significant association	97
ESR1 (6q25.1) *Estrogen receptor alpha*	XbaI	Case-control	U.S., White	88/241	+/+: 1.00 +/-: 1.39 (0.81-2.39) -/-: 1.22 (0.54-2.71)	58
		Case-control	Japan	147/266	No significant association	97
	PvuII	Case-control	U.S., White	88/241	+/+: 1.00 +/-: 1.01 (0.57-1.83) -/-: 1.60 (0.81-3.12)	58
		Case-control	Japan	147/266	No significant association	97
ESR2 (14q23.2) *Estrogen receptor beta*	RsaI	Case-control	Japan	147/266	No significant association	97
HSD3B1 (1p13) *hydroxy-delta-5-steroid dehydrogenase, 3 beta 1*	T367N (rs1047303)	Case-control	U.S., White	245/222	AA: 1.00 AC,CC: 1.50 (1.01-2.24)	117
	7062C/T	Case-control	U.S., White	245/222	CC: 1.00 CT,TT: 1.04 (0.67-1.60)	117
HSD3B2 (1p13.1) *hydroxy-delta-5-steroid dehydrogenase, 3 beta 2*	7519C/G	Case-control	U.S., White	245/222	CC: 1.00 CG,GG: 1.06 (0.66-1.69)	117
	7474C/T	Case-control	U.S., White	245/222	CC: 1.00 CT,TT: 1.17 (0.72-1.84)	117
HSD17B3 (9q22) *Hydroxysteroid (17-beta) dehydrogenase 3*	G289S (rs2066479)	Case-control	Italy	103/109	GG: 1.00 GS/SS: 2.50 (1.03-6.07)	116
HSD17B1 (17q21) *Hydroxysteroid (17 beta) dehydrogenase 1*	Haplotype tagging SNPs	Consortium nested case-control	Multiple countries, ethnicities	8301/ 9373	No overall genetic association with prostate cancer or tumor stage	118
VDR (12q12-q14) *Vitamin D receptor*	poly-A	Case-control	U.S., White	57/169	<18/<18: 1.00 All other: 4.61 (1.34-15.82)	46
		Case-control	U.S., Black	151/169	<18/<18: 1.00 <18/≥18: 0.71 (0.32, 1.59) ≥18/≥18: 0.93 (0.42, 2.06)	179
		Case-control	Europe	131/104	SS: 1.00 SL: 0.44 (0.20, 0.97) LL: 0.63 (0.27, 1.43)	181
		Case-control	Japan	100/202	LL: 1.00 SL: 1.04 (0.56, 1.94) SS: 0.63 (0.15, 2.56)	183
		Case-control	U.S., White	77/183	SS: 1.00 SL: 1.4 (0.7, 2.9) LL: 1.0 (0.5, 2.2)	185
		Case-control	U.S., Black and White	345/292	Blacks: SS: 1.00 SL: 2.0 (0.78-5.0) LL: 1.5 (0.62-3.7) Whites SS: 1.00 SL: 1.4 (0.77-2.6) LL: 1.1 (0.59-2.2)	192
		Case-control	U.S., mostly White	559/523	SS: 1.00 SL: 1.88 (0.62-1.24) LL: 1.10 (0.77-1.58)	193
	BsmI (g.60890G>A)	Case-control	U.S., Black	151/169	BB: 1.00 Bb: 0.97 (0.47, 2.03) bb: 1.13 (0.54, 2.38)	179
		Nested case-control	U.S., White	372/591	bb: 1.00 Bb: 0.82 (0.54, 1.25) BB: 0.97 (0.53, 1.78)	180
		Case-control	Japan	222/128	BB,Bb: 1.00 bb: 3.44 (2.15, 5.49)	184
		Case-control	China	191/304	bb: 1.00 Bb: 1.01 (0.54-1.90) BB: 1.06 (0.30-3.67)	186
		Case-control	Canada	483/548	bb: 1.00 bB: 0.99 (0.7-1.4) BB: 1.09 (0.8-1.5)	65
		Case-control	Japan	81/105	bb: 1.0	190

				Bb,B:	1.5 (0.8-2.9)	
	Case-control	U.S., Black and White	345/292	Blacks:		192
				bb:	1.00	
				Bb:	0.90 (0.51-1.6)	
				BB:	0.98 (0.34-2.5)	
				Whites		
				bb:	1.00	
				Bb:	1.3 (0.78-2.1)	
				BB:	0.93 (0.49-1.8)	
	Case-control	U.S., mostly White	559/523	Overall:		193
				BB:	1.00	
				Bb:	1.08 (0.79-1.48)	
				bb:	1.30 (0.94-1.80)	
				Localized disease:		
				BB:	1.00	
				Bb:	1.28 (0.88-1.86)	
				bb:	1.49 (1.02-2.17)	
	Case-control	Taiwan	160/205	bb:	1.00	194
				Bb,BB:	0.50 (0.25-0.98)	
	Case-control	Australia	812/713	bb:	1.00	196
				bB,BB:	1.17 (0.69-1.99)	
TaqI (rs731236)	Case-control	U.S., White	108/170	TT,Tt:	1.00	178
				tt:	0.34 (0.16-0.76)	
	Nested case-control	U.S., White	372/591	TT:	1.00	180
				Tt:	0.90 (0.59, 1.38)	
				tt:	1.12 (0.61, 2.07)	
	Case-control	Europe	131/104	TT:	1.00	181
				Tt:	0.50 (0.27, 0.92)	
				tt:	1.15 (0.48, 2.74)	
	Case-control	Japan	66/60	Tt,tt:	1.00	182
				TT:	1.32 (0.62,2.83)	
	Case-control	Japan	100/202	TT:	1.00	183
				Tt:	1.04 (0.56, 1.95)	
				tt:	0.63 (0.16, 2.58)	
	Case-control	Japan	222/128	Tt,tt:	1.00	184
				TT:	1.28 (NS)	
	Case-control	U.S., White	77/183	tt:	1.0	185
				Tt:	1.6 (0.8, 3.4)	
				TT:	1.1 (0.5, 2.4)	
	Case-control	Portugal	163/211	tt:	1.00	189
				Tt,TT:	1.87 (1.02-3.37)	
	Case-control	Austria	190/190	TT:	1.00	187
				tt:	1.76 (0.90-3.45)	
	Case-control	Japan	110/90	TT associated with risk of aggressive disease		188
	Case-control	Japan	81/105	TT:	1.0	190
				Tt,tt:	1.4 (0.7-2.8)	
	Case-control	U.S., Black and White	345/292	Blacks		192
				tt:	1.00	
				Tt:	0.88 (0.34-2.3)	
				TT:	0.94 (0.37-2.4)	
				Whites		
				tt:	1.00	
				Tt:	1.4 (0.75-2.5)	
				TT:	1.1 (0.57-2.1)	
	Case-control	Taiwan	160/205	TT:	1.00	194
				Tt,tt:	0.66 (0.33-1.31)	
	case-control	Brazil, mixed	165/200	No association observed		191
	Case-control	U.K., mixed	267/795	tt:	1.00	70
				Tt:	0.93 (0.59-1.46)	
				TT:	0.91 (0.65-1.28)	
FokI (g.27823C>T)	Case-control	Europe	131/104	No association observed		181
	Case-control	China	191/304	FF:	1.00	186
				Ff:	1.06 (0.69-1.63)	
				ff:	1.13 (0.67-1.91)	
	Case-control	U.S. Black and White	345/292	Blacks		192
				ff:	1.00	
				Ff:	0.59 (0.14-2.5)	
				FF:	1.2 (0.31-5.0)	
				Whites		
				ff:	1.00	
				Ff:	1.6 (0.82-3.2)	
				FF:	1.3 (0.64-2.5)	
	Case-control	U.S., mostly White	559/523	FF:	1.00	193
				Ff:	1.09 (0.83-1.42)	
				ff:	1.28 (0.90-1.82)	
	Case-control	Australia	812/713	ff:	1.00	196
				fF:	0.97 (0.78-1.20)	

					FF: 0.99 (0.72-1.35)	
		Case-control	India	128/147	Significant association of F allele with risk (p=0.003)	195
INS (11p15.5) *Insulin*	+1127 C/T 3'UTR, 9bp downstream of stop (PstI)	Case-control	U.S., mixed	178/135	CT,TT: 1.00 CC: 3.57 (1.35-9.45)	157
		Case-control	U.S., 97% White	180/255	CC: 1.0 CT,TT: 0.9 (0.6-1.3)	159
		Family-based case-control	U.S., mostly White	439/479	CC: 1.00 CT,TT: 1.06 (0.71-1.58)	160
		Case-control	U.S., Black	124/342	CC: 1.00 CT,TT: 1.59 (0.93-2.72)	158
LEP (7q31.3) *Leptin*	-2548G/A	Case-control	Portugal, White	150/118	GG: 1.00 GA: 2.11 (1.20-3.71) AA: 2.93 (1.27-6.75)	161
LEPR (1p31) *Leptin receptor*	K109R	Case-control	U.K., White	271/277	KK: 1.00 KR: 1.01 (0.69-1.48) RR: 1.36 (0.65-2.85)	162
	Q223R	Case-control	U.K., White	271/277	QQ: 1.00 QR: 0.85 (0.58-1.26) RR: 0.82 (0.52-1.29)	162
IRS1 (2q36) *Insulin receptor substrate 1*	G972R	Case-control	U.S., 97% White	191/260	GG: 1.0 GR,RR: 2.8 (1.5-5.1)	159
		Family-based case-control	U.S., mostly White	439/479	GG: 1.0 GR,RR: 1.14 (0.64-2.04)	160
IRS2 (13q34) *Insulin receptor substrate 2*	G1057D	Case-control	U.S., 97% White	177/256	GG: 1.0 GD,DD: 1.0 (0.7-1.4)	159
IGF1 (12q22-q23) *Insulin-like growth factor 1*	(CA)n	Case-control	Canada	483/548	No 19 allele: 1.00 One 19 allele: 1.46 (1.0-2.1) Two 19 alleles: 1.58 (1.1-2.3)	65
		Family-based case-control	U.S., mostly White	440/480	Allelic association: 19 allele: 1.00 <19 allele: 0.97 (0.67-1.41) >19 allele: 0.99 (0.78-1.27)	172
		Case-control	U.S., 96% White	591/538	No 19 allele: 1.00 One 19 alleles: 1.14 (0.77-1.67) Two 19 alleles: 0.94 (0.63-1.40)	169
		Case-control	U.S., 97% White	193/263	Two 19 alleles: 1.0 All other:: 1.0 (1.0-1.1)	159
		Case-control	U.S., Black and White	100/93	No 19 allele: 1.00 One 19 allele: 0.6 (0.3-1.4) Two 19 alleles: 0.3 (0.1-0.7)	170
IGF2 (11p15.5) *Insulin-like growth factor 2*	+3580 MspI	Case-control	U.S., mixed	178/135	GG: 1.00 GA: 0.90 (0.42-1.95) AA: 1.52 (0.37-6.27)	157
	ApaI (exon 2)	Case-control	Taiwan	96/121	No association observed (p=0.781)	173
IGFBP3 (7p13-p12) *Insulin-like growth factor binding protein 3*	-202A/C	Case-control	Canada	483/548	A/A: 1.00 A/C: 0.71 (0.5-0.9) C/C: 1.00 (0.7-1.3)	65
		Case-control	Japan	307/227	AA: 1.00 AC: 0.77 (0.55-1.09) CC: 0.97 (0.48-2.00)	174
		Family-based case-control	U.S., mostly White	440/480	CC: 1.00 AC: 0.81 (0.51-1.30) AA: 0.76 (0.40-1.44)	172
		Case-control	U.S., Black and White	100/93	AA: 1.00 AC: 1.9 (0.9-4.1) CC: 1.3 (0.6-3.1)	170
	Ala32Gly	Case-control	U.S., 96% White	591/538	Ala/Ala: 1.00 Ala/Gly: 0.96 (0.74-1.24) Gly/Gly: 0.89 (0.61-1.29)	169

3.4.3. CYP19

The *CYP19* gene, located in chromosome band 15q21.1, codes for the key steroidogenic enzyme aromatase, which catalyzes the irreversible conversion of androstenedione to estrone and testosterone to estradiol. Aromatase is present in the gonads and in the extragonadal organs and tissue, including the prostate and adipose tissue. In men, conversion of androgen to estrogen occurs mostly in the adipose tissue. To date, five studies have investigated the role of *CYP19* polymorphisms in prostate cancer (57, 58, 96-98). Two out of three studies report a positive association with the tetra-nucleotide repeat $(TTTA)_n$ in intron 4 (57, 96); however, the categorization of alleles and genotypes for this marker are inconsistent, and comparisons between studies are therefore difficult to make. Another study reported that the variant allele of the Arg264Cys

polymorphism in exon 7 (a C to T substitution) (58) was associated with a 72% non-significant increased risk of prostate cancer, a finding which was not confirmed in a subsequent investigation (97).

3.4.4. SRD5A2

Cross-sectional surveys show that western men have higher serum levels of 3alpha-diol G than native Japanese men (99) and higher chest hair density than Chinese men (100). Because serum levels of 3alpha-diol G and body hair reflect steroid 5alpha-reductase activity, these observations led to the hypothesis that population differences in steroid 5alpha-reductase activity and/or the polymorphisms of the *SRD5A2* gene, which encodes the type 2 steroid 5alpha-reductase enzyme, may be related to the development of prostate cancer and may contribute to part of the large racial/ethnic differences in risk (40).

More than 22 mutations, including 10 single amino acid missense substitutions, have been reported for *SRD5A2* (101). Four of these mutations -- A49T (a substitution of threonine for alanine at codon 49), V89L (a substitution of leucine for valine at codon 89), R227Q (a substitution of glutamine for arginine at codon 227), and a $(TA)_n$ dinucleotide repeat -- have been investigated for their association with prostate cancer in eighteen epidemiologic studies that have produced mixed results (Table 1) (57, 65, 68, 70, 82, 87, 102-113). Of the 11 studies investigating the A49T marker in the *SRD5A2* gene which increases enzyme activity 5-fold *in vitro* (101), just one reported a statistically significant association between the T variant and prostate cancer, and this association was only significant among U.S. Blacks (104). However, a case series reported that the A49T genotype was associated with more aggressive prostate cancer (114). In general, the results of the studies investigating the prostate cancer associations of the V89L marker (57, 65, 68, 70, 82, 87, 103, 105, 106, 108-113), which modestly reduces enzyme activity *in vitro* and *in vivo* (101) and the $(TA)_n$ repeat length marker (57, 70, 102, 105, 108, 111), which has no known functional relevance are mixed. It is interesting to note that relative to Western men, Asian men have a higher prevalence of V89L marker's LL genotype, which is associated with lower serum levels of 3alpha-diol G (101). The R227Q mutation, which is related to male pseudohermaphroditism and almost abolishes enzyme activity (101), has been detected only in Asians, and the only study investigating its role found no significant association with prostate cancer risk (108).

The inconsistent findings in the *SRD5A2* markers in various studies are largely due to the low frequency of certain mutant alleles of some markers in the *SRD5A2* gene. For example, other than the V89L mutation, the frequency of the mutant alleles in various markers (including A49T and R227Q) is less than 5%, limiting the power of detection. Nevertheless, in a recent meta-analysis, Ntais et al. concluded that overall, the T allele of the A49T marker is associated with a modest risk increase, and although evidence is less consistent, the LL genotype of the V89L marker and longer $(TA)_n$ repeats may be associated with increased risk as well (115).

3.4.5. HSD3B and HSD17B

Incomplete activation or slow catabolism of DHT within the prostate can lead to the accumulation of DHT and, perhaps, increased androgenic action. Thus, enzymes that catalyze the break down DHT may be of etiologic importance for prostate cancer. As shown in Figure 2, at least four enzymes, 17beta-hydroxysteroid dehydrogenase type I (encoded by the *HSD17B1* gene), 17beta-hydroxysteroid dehydrogenase type III (encoded by the *HSD17B3* gene), 3alpha-hydroxysteroid dehydrogenase (encoded by the *HSD3A* gene), and the 3beta-hydroxysteroid dehydrogenases (encoded by the *HSD3B1 and HSD3B2* genes located at 1p13 and 1p13.1), are involved in the metabolism of DHT within the prostate. Three studies have examined these genes. One reported a significant association of the G289S polymorphism in the *HSD17B3* gene (116) and another reported an association of the N367T marker within the *HSD3B1* gene, but no prostate cancer associations of the c7062t marker in *HSD3B1* and the c7159g and c7474t SNPs in *HSD3B2* (117). These early results are evidence for a role of these genes in prostate cancer risk, but further studies are needed. In contrast, the most recent study, a comprehensive examination of the *HSD17B1* gene, examined cases and controls from a consortium of cohort studies (118). Through a combination of large sample size (>8000 cases and >9000 controls), multiple ethnicities, and utilization of haplotype-tagging SNPs rather than single SNPs, overall this study lays out strong evidence for a lack of association of the *HSD17B1* gene with risk.

3.4.6. CYP3A4

The *CYP3A* (cytochrome P450, family 3, subfamily A) subfamily members *CYP3A4* and *CYP3A5* are located at a single locus on chromosome 7q21-q22. The *CYP3A4* gene product is involved in oxidative conversion of testosterone to the biologically less active forms 2beta-, 6beta-, and 15beta-hydroxytestosterone, and the variant *1B allele of the A-391G SNP in the 5'-upstream region has been linked to higher prostate cancer stage and grade (119). Furthermore, the striking differences in *1B frequencies between Caucasian populations and populations of African extraction (120) suggest that this SNP may be related to racial differences in prostate cancer risk. However, while one case-control study showed significant excess risk of aggressive disease with the *1B allele among African-Americans, it did not find this risk among Caucasians (121). Other studies showed a modest but non-significant reduced risk of prostate cancer in connection with the variant *1B allele (65, 122, 123). The low frequency of the variant in most populations limited the statistical power of many of these studies.

3.4.7. CYP3A5

The *CYP3A5* gene product, highly expressed in the prostate, is a major contributor to the metabolic clearance of many CYP3A substrates, including drugs and other xenobiotic compounds, as well steroid hormones. A number of polymorphic markers have been identified in the *CYP3A5* gene, two of which have been studied in epidemiologic studies of prostate cancer. The *CYP3A5**1

marker, whose variant allele may promote inactivation of testosterone (124), was found to have a borderline significant association with reduced risk of prostate cancer in one study (122) but not another (123). The variant allele of a different marker, *CYP3A5**3, results in a truncated and presumably less functional protein (125), supporting the observation in a Japanese population that the *CYP3A5**3 wild-type allele was associated with reduced prostate cancer risk (124).

4. ESTROGENS AND ESTROGEN RECEPTORS

4.1. Estrogens in Prostate Cancer

The prostate obtains estrogens from peripheral sources (such as adipose tissue) and through stromal conversion of testosterone. Although estrogens are used as anti-androgens in the treatment of prostate cancer, their etiologic role is unclear. Several lines of evidence suggest that estrogens may enhance prostate carcinogenesis. Estrogens interact with SHBG and androgen to regulate normal prostate growth and function (126), and mediate epithelial cell responses to androgens via the IGF pathway (127). Induction of prostate tumors in laboratory rats by testosterone administration is considerably enhanced by the addition of estradiol (128). In addition, prenatal exposure to extremely low doses of diethylstilbestrol (DES) and other estrogenic compounds in the presence of androgen significantly affects rodent prostate development *in vivo* and *in vitro* (129), leading to imprinting and increased estrogen sensitivity later in life (5). Finally offspring of DES-exposed mothers have an elevated risk of prostate cancer (130).

Together, these data suggest that estrogens may increase the risk of prostate cancer. While Gann et al. (16) found that higher levels of serum estradiol were associated with a reduced risk of prostate cancer, it is unclear whether physiologic or pharmacologic estrogen doses were used in this study. It is possible that at physiologic doses, estrogens have anti-tumor effects via the hypothalamic-pituitary-gonadal axis, while at pharmacologic levels, estrogens work alone or in conjunction with androgens to promote tumor growth.

4.2. Estrogen Receptors in Prostate Cancer

Estrogen receptors (ERs) mediate the biologic effect of estrogen in target tissue (131). It has been suggested that the concentrations of the two distinct ERs, ER-alpha and ER-beta, may affect prostate cancer risk through the influence of the estrogen-ER complex on AR concentration (132, 133). Although most molecular studies show evidence of ER-alpha expression in prostate stromal cells, ER-alpha is not considered to be highly expressed in prostate carcinoma. On the other hand, the more recently discovered ER-beta is highly expressed in prostatic epithelium (131). In addition, ER-beta may be involved in the regulation of AR content in the prostate and in epithelial growth, and may thus serve as a physiologic regulator of prostatic epithelial growth and differentiation (134). The role of estrogens in prostate carcinogenesis is still unclear; however evidence is mounting that this role may be a fertile area for additional research.

4.3. Estrogen-Related Genes

Estrogen receptor-alpha, coded by the *ESR1* gene, has been examined in two studies (58, 97), both of which showed no association of the *ESR1* XbaI and PvuII restriction fragment length polymorphism (RFLP) markers. However, the first study did observe significant 3- to 5-fold excess risks among subgroups defined by both the *ESR1* markers and *AR* repeat lengths. Just one study has examined the risk of prostate cancer associated with ER-beta, encoded by the *ESR2* gene, and found no significant association of the RsaI RFLP marker (97).

5. SEX HORMONE-BINDING GLOBULIN (SHBG)

5.1. Role of SHBG in Sex Hormone Transport

Sex hormone-binding globulin (SHBG) transports androgens and estrogens in the circulation. In the only study to report a definitive positive association between serum levels of testosterone and prostate cancer, Gann et al. (16) found no statistically significant association between prostate cancer risk and testosterone before controlling for serum levels of SHBG. After adjusting for androgen and estradiol, Gann et al. found that serum levels of SHBG were associated with a 54% reduced risk of prostate cancer (16). Although it is not entirely clear whether adjustment for SHBG is the best approach to assess the independent effect of testosterone, the Gann et al. study showed that the effect of serum testosterone was more pronounced after adjustment for SHBG.

5.2. Role of SHBG in Prostate Cancer

Recent data suggest that SHBG may have an effect on carcinogenesis that is independent of its function as a regulator of the free fraction of androgen and estrogen. For example, SHBG mediates steroid hormone signal transduction at the plasma membrane, thereby allowing certain steroid hormones to act without entering the cell by interacting with SHBG membrane receptors (135). In addition, estradiol can activate the AR by using SHBG as an intermediate (136). However, this pathway is complex and not well understood, and the potential independent effects of SHBG have not been investigated fully. Because several factors, including estrogens, androgens, thyroid hormones, insulin, leptin, and IGF1 affect circulating levels of SHBG (137-140), future studies should measure SHBG along with several other hormones and evaluate its independent effect on prostate cancer risk.

6. INSULIN AND LEPTIN

6.1. Circulating Insulin and Leptin Levels and Prostate Cancer

Serum levels of insulin and leptin are associated with obesity and body fat distribution, two putative risk factors for prostate cancer (141, 142). The roles of insulin and leptin in prostate carcinogenesis have been investigated in three case-control studies (143-145). Two of these studies, both case-control investigations, reported no association of serum leptin with prostate cancer risk (143, 144), while the nested case-control study from Sweden found a positive association (145). In addition, a recent clinical survey (146) showed that higher plasma levels of leptin were associated with larger (>0.5 cm3) prostate tumor volumes. Furthermore, one of the two case-

control studies also reported a positive association with serum levels of insulin (144). This association was independent of overall and abdominal obesity as well as serum levels of IGFs, sex hormones, and leptin. Serum levels of C-peptide, a marker of insulin secretion from pancreatic beta cells, were found to be associated with aggressive prostate cancer in a recent prospective study (147).

Insulin's primary mode of stimulating cell growth is through binding to the insulin receptor and activating a cascade of post-receptor events involved in cell survival and proliferation (148-150). Insulin may also affect prostate tumorigenesis through several other potential pathways, including the obesity-sex-hormone pathway, the IGF pathway, the PI3-kinase (phosphatidylinositol 3'-kinase) signaling pathway, and the apoptotic pathway. In the obesity-sex-hormone pathway, insulin increases the transcription of *CYP17* (the gene encoding the enzyme critical to the biosynthesis of testosterone) and decreases the synthesis of SHBG (151, 152), thereby increasing the bioavailability of free testosterone for uptake by the prostate gland. In addition, insulin can regulate aromatase activity, thus influencing the conversion of androgens to estrogens (153, 154). Because of the high degree of homology between insulin and IGF (50% amino acid homology and 60% receptor homology), insulin can bind to the type I IGF receptor and initiate IGF-mediated growth (155). Insulin can also inhibit transcription of IGF binding protein 1, thereby increasing unbound circulating IGF1 (155). In recent studies, higher circulating levels of IGF1 have been linked to an increased risk of prostate cancer (156). Although epidemiologic evidence for the association between insulin and prostate cancer is preliminary, the roles of insulin and leptin need to be clarified further because they may help explain the strong differences in prostate cancer incidence across populations.

6.2. Insulin and Leptin Genes

To date, four studies have examined variants of the insulin gene with risk of prostate cancer, and all have been conducted in U.S. subjects. (157-160). Two of these four studies (157, 158) show excess risk associated with the CC genotype of the PstI marker in the *INS* gene, which encodes insulin. In addition, one of the two studies that have examined the role of insulin receptor substrate (IRS)1 (159, 160) shows an association with the *IRS1* G972R marker (159), while the single study examining *IRS2* shows no prostate cancer risk associated with the G1079D marker (159). The only study of the leptin gene *LEP* showed a strong association with prostate cancer risk in Portuguese Whites, an effect that was even more pronounced for advanced stage disease (161). However, the only study of the leptin receptor gene *LEPR* showed no association of two markers with early onset prostate cancer in the United Kingdom (162). Genetic studies of the association of the insulin and leptin axis with prostate cancer are still in the early phases, and evidence will continue to accumulate.

7. INSULIN-LIKE GROWTH FACTOR (IGF) AXIS

7.1. IGF Axis and Prostate Cancer

IGF1 and IGF2 are polypeptides that function as both tissue growth factors and endocrine hormones, with strong mitogenic and anti-apoptotic effects on prostate epithelial cells. The six known IGF binding proteins (IGFBPs) are able to bind to IGFs, thus preventing the activation of IGF receptors. Over a dozen studies, both retrospective and prospective, have examined the role of circulating elements of the IGF axis in prostate cancer. Overall, the evidence suggests that higher IGF1 levels are associated with increased risk of prostate cancer (156, 163-167), and that this association is strongest for advanced disease (163, 165, 166). In contrast, although the evidence is not as consistent, increasing levels of IGFBP3, and possibly IGFBP1, appear to be associated with decreased prostate cancer risk (163, 168). The evidence for involvement of the IGF axis in prostate cancer is compelling, and should be a fruitful area for future research.

7.2. IGF Axis Genes

The genes encoding IGF1, IGF2, and IGFBP3 have been studied with regard to prostate cancer risk. A CA tandem repeat polymorphism in the *IGF1* gene has been linked to prostate cancer risk in most (65, 169-171), but not all published studies (159, 172). In contrast, the studies of the *IGF2* MspI marker (157) and the *IGF2* ApaI marker (173), as well as all studies of markers in the *IGFBP3* gene (65, 169, 170, 172, 174) have been null. Investigation of IGF-related genetic markers in prostate cancer risk is still in its early phases, and data are still accumulating.

8. VITAMIN D

8.1. Vitamin D and Prostate Cancer

Vitamin D is a steroid hormone synthesized primarily in skin in response to sunlight exposure. Vitamin D and its analogs have potent anti-proliferative, pro-differentiative, and pro-apoptotic effects on prostate cancer cells *in vitro* (175), and vitamin D inhibits prostate tumor growth *in vivo* (176). A clinical trial of calcitriol, the most biologically active ligand for the vitamin D receptor (VDR), is currently underway to investigate additive anti-neoplastic activity with docetaxel in men with advanced hormone refractory prostate cancer (177). However, despite the strong and consistent laboratory evidence linking vitamin D to prostate cancer, five prospective studies investigating serum levels of vitamin D and prostate cancer risk have produced inconsistent results (6).

8.2. Vitamin D Receptor (VDR) Gene

The strong laboratory evidence linking vitamin D to prostate cancer paved the way for a number of epidemiologic studies of the *VDR* gene, the primary mediator of vitamin D's physiologic action. However, despite promising early results, 21 studies of the 3' poly-A, TaqI, BsmI, and ApaI polymorphic markers, as well as the functional 5' FokI marker, in a variety of populations show mixed results (46, 65, 70, 178-196). A recent meta-analysis (197) concludes that there is no evidence of association of the *VDR* gene with prostate cancer.

9. GONADOTROPINS

Gonadotropins, including luteinizing hormone (LH), follicle-stimulating hormone, and prolactin, are secreted by the pituitary and are involved in feedback

control of testosterone, and gonadotropin-releasing hormone agonists are used to treat prostate cancer. Gonadotropins are not routinely measured in epidemiologic studies because their levels are influenced by pulsatile secretion and diurnal variation, which complicate their measurement and thus the assessment of their roles in prostate cancer. Data from one study has suggested that higher serum levels of LH, in concert with testosterone, may be associated with an increased risk of prostate cancer risk (29). Prolactin mediates the entry of testosterone into prostatic cells *in vitro* and *in vivo* (198). However, there are not many epidemiologic studies examining the role of circulating prolactin in prostate cancer (16, 29, 37, 199). The biological relevance of gonadotropins to testosterone suggests that their roles in prostate cancer need to be clarified in future studies.

10. FUTURE DIRECTIONS

Prostate cancer is a complex, multi-factorial disease with a well-recognized heritable component. Hormones, particularly androgens, clearly play a role in prostate carcinogenesis. However, despite a great deal of investigation using a variety of approaches, this role is not yet completely clear, due to a number of shortcomings. The following section describes how these shortcomings can be addressed in the future.

10.1. Studies of Hormones in Prostate Tissue

It is as yet unclear how circulating hormone levels relate to intra-prostatic levels, and whether intra-prostatic metabolism is more relevant to the etiology of prostate cancer than serologic measurements. To shed light on this, methodological studies should be carried out to collect high quality normal prostate tissue specimens for the measurement of tissue hormones, enzymatic activities, and receptor proteins. For androgens, this could result in the derivation of an overall serological index of intra-prostatic androgenicity. In addition, validated tissue hormone assays can be used to assess whether smoking, alcohol use, body size, and other lifestyle factors affect tissue levels of hormones. Racial or ethnic differences in tissue levels of hormones should also be evaluated after taking into account lifestyle and other potential confounding factors. It would also be useful to correlate tissue levels of hormones with genetic variants to provide insights into the functional significance of these polymorphic markers. To do so, peripheral lymphocytes or buccal cells should also be collected from study participants so that DNA may be extracted and genotyped for relevant polymorphisms in hormone-metabolizing genes.

10.2. Studies of Hormones in Circulation

Because it is often infeasible to measure tissue hormone levels in observational epidemiological studies, future studies, particularly nested case-control studies, will continue to rely on serum-based assays of hormone levels. Clearly, in case-control studies, careful measures should be taken to minimize variation in assays and blood sampling. These measures should include the use of sensitive and specific assays to minimize measurement error, as well as simultaneous measurement of several hormones in the same study to provide a more complete hormonal profile of each study subject so that the net effect of each hormone can be assessed. For example, liquid or gas chromatography-mass spectroscopy (GC-MS) assay methods can be used to derive a complete profile of androgen and estrogen metabolites, which may help provide insight into whether other androgen metabolites more accurately reflect tissue levels of androgens, leading to more reliable and accurate assessment of the relationships between sex steroids and prostate cancer. Furthermore, blood collection times should be standardized so that diurnal and seasonal variation in hormone levels among study subjects can be minimized, and investigators should use large enough sample sizes (preferably several hundred case-control pairs from prospective studies) to yield sufficient statistical power.

Analytically, it is important to stratify results by stage and/or grade, as risk factors for more aggressive disease may differ from those of less-aggressive disease. In addition, it is important to have a better understanding of factors that affect circulating levels of hormones so that appropriate statistical analyses can be conducted to control for confounding. For example, methodological studies examining relationships between epidemiologic factors, such as anthropometry, physical activity, or diet, and the interrelationships among hormones, including androgens, estrogens, IGFs, SHBG, leptin, and insulin, should be carried out to provide critical data to help refine the analytical models in the statistical analyses. In addition, one of the concerns of retrospective studies is that hormone measurements may be influenced by disease. To address this, results from retrospective studies should be interpreted only in the context of supportive prospective data. Because the validity of the results hinges on the quality of hormone assays, we cannot stress enough the importance of optimizing hormone measurements in future studies. Imperfect as they may be, serum levels of hormones, if measured accurately, presumably reflect the combined effects of studied genetic polymorphisms as well as effects of other genes and exogenous factors, and can provide valuable clues to the role of hormones in prostate cancer risk.

A better understanding of how serum hormone levels vary in different racial and ethnic populations at varying prostate cancer risk may shed light on the etiology of prostate cancer. In addition, studies that measure the levels of circulating hormones in various decades of life may help identify critical time periods in life that are etiologically relevant to prostate cancer risk. Because levels of circulating testosterone in pregnant black women are higher than those in pregnant white women, it has been suggested that *in utero* exposure to testosterone may explain the excess prostate cancer risk in African American men (200). Comparisons of hormone levels in cord blood from various racial/ethnic groups may provide additional insights into this hypothesis. These suggested methodological studies, although cross-sectional in nature, should be guided by sound epidemiologic principles and include probability samples from each population in order

to aid in the interpretation of results.

10.3. Studies of Genes

The characterization of hormone metabolizing genes provides an opportunity to examine disease at the level of germline susceptibility. Compared to serum-based studies, this approach has two distinct advantages. First, genetic assays usually, but not always, produce more qualitative (categorical) results with higher reproducibility than the continuous data typically produced by serologic assays. Second, unlike serologic markers in cross-sectional case-control studies, genetic susceptibility status (i.e., genotype) is not affected by the presence or process of disease or by other exposures that may change over time. Despite these advantages, there are serious limitations to studies of genetic polymorphisms and prostate cancer risk.

Incomplete gene coverage is a major problem in many studies. Most studies of genetic associations to date have focused on a small number of variants and candidate genes, often genes that are related to one another or in a common pathway. In an attempt to assess the overall association of these genes with prostate cancer, study subjects are typically genotyped for 5-10 candidate polymorphisms within these genes. However, the polymorphisms known to exist within the gene often number in the hundreds or thousands. Thus, most studies to date have assessed but a small fraction of the genetic variation within a given gene. Accordingly, observed associations may in fact be due to linkage with a true causal marker elsewhere in the region. Functional data on a marker can help improve the interpretation of such results, but they are rarely available. In addition to these concerns about false positive results for individual markers, it is important to note that failure to observe an association of studied markers when gene coverage is incomplete can also lead to falsely concluding that the studied gene is not associated with disease (false negatives). To address these concerns, studies are now incorporating more SNPs into their genetic panels. In addition, studies are taking advantage of recent advances in identification of haplotype tagging SNPs and haplotype estimation techniques that have improved our ability to study the influence of genes on disease risk knowing that some fixed percentage of the gene's diversity is being assessed, while concomitantly minimizing the number of SNPs that must be typed. Data from the Human Genome Project and the International HapMap Project (www.hapmap.org) have become useful in this aspect, and when paired with recent advances in informatics tools, these may permit a more comprehensive interrogation of genetic loci of interest. Functional considerations, however, also should be kept in mind.

Multiple comparisons is also a serious and growing issue in genetic epidemiology studies, due in large part to recent advances in technology that enable rapid collection of vast amounts of genotyping data. For example, many studies now routinely examine 20 or more SNPs in each of perhaps 5-10 genes, resulting in over 100-200 individual comparisons in a single analysis. By chance alone, 5-10 of these comparisons are likely to be positive. Thus, without pre-specified hypotheses, many observed findings are likely to be false positive results. This is especially true for common, low penetrance markers, as these are unlikely to have strong true risk estimates. Although statistical corrections including Bonferroni and Sidak tests, or Bayesian approaches such as the False Positive Report Probability (201) have been employed in some studies, the issue of false positives remains a major one in the literature.

Despite the concerns about false positives and false negatives, studies of individual markers within genes continue to be an important source of new leads for prostate cancer etiology research, particularly for new hypotheses involving the interplay of genetic and environmental factors. Statistical approaches to addressing false positives aside, replication of findings in studies involving different designs and populations is the most compelling evidence that an association is real. It should be noted that replication is necessary not only for positive results, but for null results as well.

Lack of sufficient statistical power is another concern. Most current studies have limited power to detect effects of rare (<5%) alleles, due to relatively small numbers of subjects (usually fewer than 500). Furthermore, even if a study has satisfactory power to examine the main effects of a single genetic locus, it rarely has sufficient power to evaluate the combined effect of several genes, or of genes with other exposures. Thus, most individual studies cannot produce a comprehensive picture of genetic predisposition and cancer risk.

Due to the large number of often mixed studies, an important need in the field is a high-quality synthesis of the literature. For prostate cancer, there are a number of rigorously conducted meta-analyses, as shown in Table 1. Such reviews can be extremely helpful in examining the totality of available evidence for a given locus. However, unpublished work, which often tends to show null results, is difficult to include in such syntheses. One answer to this is the formation of consortia of existing studies (202). Not only can these groups improve the field by planning at the outset to replicate results, positive or null, from one participating study, but they can conduct pooled analyses of individual-level data, thereby improving upon the study-level summaries of most meta-analyses. Such consortia have been formed in other areas, most notably non-Hodgkins lymphoma (203).

In addition, risk estimates can be influenced by latent ancestral differences between cases and controls that may confound the observed association, often called population stratification (204). While there is debate on the magnitude of the impact of population stratification on disease associations, methods for addressing population stratification are available, including the recently proposed use of ancestry informative genetic markers, wherein the ancestral background of each individual is assessed using a validated panel of markers and incorporated into regression modeling (205). Family based association studies are also useful in guarding against population stratification, but due to the late onset of prostate cancer (indeed, of most cancers

of any site) the use of designs that require participation and genotyping of parents and/or siblings is impractical.

Prostate cancer is a complex disease likely involving interplay of multiple risk factors, thus it is unlikely that a single common polymorphism will have a profound effect on androgen levels or prostate cancer risk. Instead, alterations in multiple susceptibility genes may be required to heighten prostate cancer risk. Many of the studies to date have examined a single aspect of hormone pathways, as opposed to an integrated examination of the interplay of several factors simultaneously. Recent advances in bioinformatics and statistical techniques, including pathway-based SNP selection strategies implemented in GenMAPP (Gene Map Annotator and Pathway Profiler (206), as well as hierarchical regression modeling (207) and multifactor dimensionality reduction (208) may help in clarifying the joint effects of multiple genetic and hormonal risk factors in prostate cancer risk.

An emerging trend in epidemiology studies is the use of whole genome approaches to scan hundreds of thousands of SNPs in large numbers of cases and controls to identify disease genes in the absence of a specific hypothesis. Multiple testing issues abound here, but through adoption of sequential marker screening strategies, and with sufficient samples sizes, such approaches may capture major variants that are highly related to endpoint of interest, such as prostate cancer. A good example of this is the NCI Cancer Genetic Markers of Susceptibility Study (http://cgems.nci.nih.gov/), which plans to scan more than 550,000 SNPs in prostate cancer cases and controls from at least five independent studies. The initial scan of 550,000 SNPs will be conducted on 1,200 cases and 1,200 controls, and is expected to show an estimated 20,000 SNPs with positive associations at $p<0.05$. These SNPs will then be confirmed in independent sub-samples of the sample set, and the approximately 25-30 SNPs that are consistently related to prostate cancer in all studies will undergo extensive investigation, including sequencing and functional studies, to provide further insight for prostate cancer etiology. This approach is expensive but is likely to provide credible evidence on a number of major loci with robust association with prostate cancer risk in several populations as a result of the replication process.

An effective means of addressing several of the shortcomings noted above is to explore hormones and hormone-related loci in large (several thousand cases) prospective studies with high-quality biological specimens and exposure assessments. We suggest that a large set of common polymorphisms of susceptibility genes involved in hormone pathways be assessed simultaneously in such studies. Furthermore, since prostate cancer is likely to result from a complex interplay of genetic and environmental factors (209) and since the expression of genetic traits is likely to be influenced by exogenous factors, investigation of interactions between genes and environmental/lifestyle factors should be conducted in large study populations with sufficient statistical power. One good example of such a large study is the Prostate Cancer Cohort Consortium (http://epi.grants.cancer.gov/BPC3/), a collaboration of dozens of large, prospective cohorts, which to date has assembled over 9,000 cases of prostate cancer for joint study and plans to utilize a candidate gene approach (210). Results from the combined analysis of these cohorts will help clarify the role of hormones in prostate cancer risk, and provide a more complete view of genetic predisposition to prostate cancer and identify susceptible subgroups for early detection.

11. SUMMARY

In summary, although many pieces of the puzzle in our understanding of the role played by hormones in prostate cancer are still missing, promising clues are emerging. A wealth of new data, including hormone levels in various biological samples, combined with an exciting new array of genetic information, is becoming available and may soon reveal more specific exposure-disease relationships that will enhance our understanding of hormonal carcinogenesis in prostate cancer. Such efforts, however, require a concerted interdisciplinary approach that combines the efforts of investigators across several disciplines, including epidemiology, urology, pathology, biochemistry, endocrinology, genetics, and molecular biology. In addition, it requires large epidemiologic study populations, such as those being achieved now by large consortia. Such studies will provide unique opportunities to incorporate state-of-the-art techniques to test emerging hypotheses in a timely fashion.

12. REFERENCES

1. Jemal, A., R. Siegel, E. Ward, T. Murray, J. Xu, C. Smigal & M. J. Thun: Cancer statistics, 2006. *CA Cancer J Clin*, 56, 106-30 (2006)
2. Huggins, C. & C. V. Hodges: Studies on prostatic cancer: Effect of castration, of estrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res.*, 1, 293-297 (1941)
3. Noble, R. L.: The development of prostatic adenocarcinoma in Nb rats following prolonged sex hormone administration. *Cancer Res*, 37, 1929-33. (1977)
4. Richie, J. P.: Anti-androgens and other hormonal therapies for prostate cancer. *Urology*, 54, 15-8 (1999)
5. Harkonen, P. L. & S. I. Makela: Role of estrogens in development of prostate cancer. *J Steroid Biochem Mol Biol*, 92, 297-305 (2004)
6. Zhao, X. Y. & D. Feldman: The role of vitamin D in prostate cancer. Steroids, 66, 293-300. (2001)
7. Freedland, S. J., E. Giovannucci & E. A. Platz: Are findings from studies of obesity and prostate cancer really in conflict? Cancer Causes Control, 17, 5-9 (2006)
8. Pasquali, R., F. Casimirri, S. Cantobelli, N. Melchionda, A. M. Morselli Labate, R. Fabbri, M. Capelli & L. Bortoluzzi: Effect of obesity and body fat distribution on sex hormones and insulin in men. Metabolism, 40, 101-4 (1991)
9. Hsing, A. W., J. K. Reichardt & F. Z. Stanczyk: Hormones and prostate cancer: current perspectives and future directions. Prostate, 52, 213-35. (2002)
10. Carter, B. S., G. D. Steinberg, T. H. Beaty, B. Childs & P. C. Walsh: Familial risk factors for prostate cancer. *Cancer Surv*, 11, 5-13 (1991)

11. Lichtenstein, P., N. V. Holm, P. K. Verkasalo, A. Iliadou, J. Kaprio, M. Koskenvuo, E. Pukkala, A. Skytthe & K. Hemminki: Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*, 343, 78-85. (2000)
12. Hirschhorn, J. N., K. Lohmueller, E. Byrne & K. Hirschhorn: A comprehensive review of genetic association studies. *Genet Med*, 4, 45-61 (2002)
13. Thigpen, A. E., D. L. Davis, A. Milatovich, B. B. Mendonca, J. Imperato-McGinley, J. E. Griffin, U. Francke, J. D. Wilson & D. W. Russell: Molecular genetics of steroid 5 alpha-reductase 2 deficiency. *J Clin Invest*, 90, 799-809 (1992)
14. Pardridge, W. M.: Plasma protein-mediated transport of steroid and thyroid hormones. *Am J Physiol*, 252, E157-64 (1987)
15. Hryb, D. J., M. S. Khan, N. A. Romas & W. Rosner: The control of the interaction of sex hormone-binding globulin with its receptor by steroid hormones. *J Biol Chem*, 265, 6048-54 (1990)
16. Gann, P. H., C. H. Hennekens, J. Ma, C. Longcope & M. J. Stampfer: Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst*, 88, 1118-26. (1996)
17. Horton, R. & R. Lobo: Peripheral androgens and the role of androstanediol glucuronide. *Clin Endocrinol Metab*, 15, 293-306 (1986)
18. Horton, R.: Dihydrotestosterone is a peripheral paracrine hormone. *J Androl*, 13, 23-7 (1992)
19. Stanczyk, F. Z., E. C. Skinner, S. Mertes, M. F. Spahn, R. A. Lobo & R. K. Ross: Alterations in circulating levels of androgens and PSA during treatment with Finasteride in men at high risk for prostate cancer. In: Hormonal carcinogenesis II. Eds: J. J. Li, S. A. Li, J. Gustafsson, S. Nandi&L. I. Sekely. Springer-Verlag, New York (1996)
20. Kokontis, J. M. & S. Liao: Molecular action of androgen in the normal and neoplastic prostate. *Vitam Horm*, 55, 219-307 (1999)
21. Culig, Z., A. Hobisch, G. Bartsch & H. Klocker: Expression and function of androgen receptor in carcinoma of the prostate. *Microsc Res Tech*, 51, 447-55 (2000)
22. Culig, Z., A. Hobisch, M. V. Cronauer, C. Radmayr, A. Hittmair, J. Zhang, M. Thurnher, G. Bartsch & H. Klocker: Regulation of prostatic growth and function by peptide growth factors. *Prostate*, 28, 392-405 (1996)
23. Gnanapragasam, V. J., P. J. McCahy, D. E. Neal & C. N. Robson: Insulin-like growth factor II and androgen receptor expression in the prostate. *BJU Int*, 86, 731-5 (2000)
24. Yeh, S. & C. Chang: Cloning and characterization of a specific coactivator, ARA70, for the androgen receptor in human prostate cells. *Proc Natl Acad Sci U S A*, 93, 5517-21 (1996)
25. Yeh, S., H. C. Chang, H. Miyamoto, H. Takatera, M. Rahman, H. Y. Kang, T. H. Thin, H. K. Lin & C. Chang: Differential induction of the androgen receptor transcriptional activity by selective androgen receptor coactivators. *Keio J Med*, 48, 87-92 (1999)
26. Park, J. J., R. A. Irvine, G. Buchanan, S. S. Koh, J. M. Park, W. D. Tilley, M. R. Stallcup, M. F. Press & G. A. Coetzee: Breast cancer susceptibility gene 1 (BRCAI) is a coactivator of the androgen receptor. *Cancer Res*, 60, 5946-9 (2000)
27. Parsons, J. K., H. B. Carter, E. A. Platz, E. J. Wright, P. Landis & E. J. Metter: Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. *Cancer Epidemiol Biomarkers Prev*, 14, 2257-60 (2005)
28. Nomura, A., L. K. Heilbrun, G. N. Stemmermann & H. L. Judd: Prediagnostic serum hormones and the risk of prostate cancer. *Cancer Res*, 48, 3515-7 (1988)
29. Hsing, A. W. & G. W. Comstock: Serological precursors of cancer: serum hormones and risk of subsequent prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 2, 27-32 (1993)
30. Platz, E. A., M. F. Leitzmann, N. Rifai, P. W. Kantoff, Y. C. Chen, M. J. Stampfer, W. C. Willett & E. Giovannucci: Sex steroid hormones and the androgen receptor gene CAG repeat and subsequent risk of prostate cancer in the prostate-specific antigen era. *Cancer Epidemiol Biomarkers Prev*, 14, 1262-9. (2005)
31. Chen, C., N. S. Weiss, F. Z. Stanczyk, S. K. Lewis, D. DiTommaso, R. Etzioni, M. J. Barnett & G. E. Goodman: Endogenous sex hormones and prostate cancer risk: a case-control study nested within the Carotene and Retinol Efficacy Trial. *Cancer Epidemiol Biomarkers Prev*, 12, 1410-6. (2003)
32. Nomura, A. M., G. N. Stemmermann, P. H. Chyou, B. E. Henderson & F. Z. Stanczyk: Serum androgens and prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 5, 621-5 (1996)
33. Guess, H. A., G. D. Friedman, M. C. Sadler, F. Z. Stanczyk, J. H. Vogelman, J. Imperato-McGinley, R. A. Lobo & N. Orentreich: 5 alpha-reductase activity and prostate cancer: a case-control study using stored sera. *Cancer Epidemiol Biomarkers Prev*, 6, 21-4 (1997)
34. Vatten, L. J., G. Ursin, R. K. Ross, F. Z. Stanczyk, R. A. Lobo, S. Harvei & E. Jellum: Androgens in serum and the risk of prostate cancer: a nested case-control study from the Janus serum bank in Norway. *Cancer Epidemiol Biomarkers Prev*, 6, 967-9 (1997)
35. Dorgan, J. F., D. Albanes, J. Virtamo, O. P. Heinonen, D. W. Chandler, M. Galmarini, L. M. McShane, M. J. Barrett, J. Tangrea & P. R. Taylor: Relationships of serum androgens and estrogens to prostate cancer risk: results from a prospective study in Finland. *Cancer Epidemiol Biomarkers Prev*, 7, 1069-74 (1998)
36. Heikkila, R., K. Aho, M. Heliovaara, M. Hakama, J. Marniemi, A. Reunanen & P. Knekt: Serum testosterone and sex hormone-binding globulin concentrations and the risk of prostate carcinoma: a longitudinal study. Cancer, 86, 312-5 (1999)
37. Mohr, B. A., H. A. Feldman, L. A. Kalish, C. Longcope & J. B. McKinlay: Are serum hormones associated with the risk of prostate cancer? Prospective results from the Massachusetts Male Aging Study. Urology, 57, 930-5. (2001)
38. Fears, T. R., R. G. Ziegler, J. L. Donaldson, R. T. Falk, R. N. Hoover, F. Z. Stanczyk, J. B. Vaught & M. H. Gail: Reproducibility studies and interlaboratory concordance for androgen assays of male plasma hormone levels. Cancer Epidemiol Biomarkers Prev, 11, 785-9 (2002)
39. Aumuller, G.: Postnatal development of the prostate. *Bull Assoc Anat* (*Nancy)*, 75, 39-42 (1991)

40. Ross, R. K., M. C. Pike, G. A. Coetzee, J. K. Reichardt, M. C. Yu, H. Feigelson, F. Z. Stanczyk, L. N. Kolonel & B. E. Henderson: Androgen metabolism and prostate cancer: establishing a model of genetic susceptibility. *Cancer Res*, 58, 4497-504. (1998)
41. Culig, Z., A. Hobisch, A. Hittmair, H. Peterziel, C. Radmayr, G. Bartsch, A. C. Cato & H. Klocker: Hyperactive androgen receptor in prostate cancer: what does it mean for new therapy concepts? *Histol Histopathol*, 12, 781-6 (1997)
42. Chamberlain, N. L., E. D. Driver & R. L. Miesfeld: The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. *Nucleic Acids Res*, 22, 3181-6 (1994)
43. Edwards, A., H. A. Hammond, L. Jin, C. T. Caskey & R. Chakraborty: Genetic variation at five trimeric and tetrameric tandem repeat loci in four human population groups. *Genomics*, 12, 241-53 (1992)
44. Sawaya, M. E. & A. R. Shalita: Androgen receptor polymorphisms (CAG repeat lengths) in androgenetic alopecia, hirsutism, and acne. *J Cutan Med Surg*, 3, 9-15 (1998)
45. Hoffmann, R. & R. Happle: Current understanding of androgenetic alopecia. Part I: etiopathogenesis. *Eur J Dermatol*, 10, 319-27 (2000)
46. Ingles, S. A., R. K. Ross, M. C. Yu, R. A. Irvine, G. La Pera, R. W. Haile & G. A. Coetzee: Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor. *J Natl Cancer Inst*, 89, 166-70. (1997)
47. Giovannucci, E., M. J. Stampfer, K. Krithivas, M. Brown, D. Dahl, A. Brufsky, J. Talcott, C. H. Hennekens & P. W. Kantoff: The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. *Proc Natl Acad Sci U S A*, 94, 3320-3. (1997)
48. Stanford, J. L., J. J. Just, M. Gibbs, K. G. Wicklund, C. L. Neal, B. A. Blumenstein & E. A. Ostrander: Polymorphic repeats in the androgen receptor gene: molecular markers of prostate cancer risk. *Cancer Res*, 57, 1194-8. (1997)
49. Platz, E. A., E. Giovannucci, D. M. Dahl, K. Krithivas, C. H. Hennekens, M. Brown, M. J. Stampfer & P. W. Kantoff: The androgen receptor gene GGN microsatellite and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev*, 7, 379-84. (1998)
50. Correa-Cerro, L., G. Wohr, J. Haussler, P. Berthon, E. Drelon, P. Mangin, G. Fournier, O. Cussenot, P. Kraus, W. Just, T. Paiss, J. M. Cantu & W. Vogel: (CAG)nCAA and GGN repeats in the human androgen receptor gene are not associated with prostate cancer in a French-German population. *Eur J Hum Genet*, 7, 357-62. (1999)
51. Edwards, S. M., M. D. Badzioch, R. Minter, R. Hamoudi, N. Collins, A. Ardern-Jones, A. Dowe, S. Osborne, J. Kelly, R. Shearer, D. F. Easton, G. F. Saunders, D. P. Dearnaley & R. A. Eeles: Androgen receptor polymorphisms: association with prostate cancer risk, relapse and overall survival. *Int J Cancer*, 84, 458-465 (1999)
52. Ekman, P., H. Gronberg, H. Matsuyama, M. Kivineva, U. S. Bergerheim & C. Li: Links between genetic and environmental factors and prostate cancer risk. *Prostate*, 39, 262-268 (1999)
53. Lange, E. M., H. Chen, K. Brierley, H. Livermore, K. J. Wojno, C. D. Langefeld, K. Lange & K. A. Cooney: The polymorphic exon 1 androgen receptor CAG repeat in men with a potential inherited predisposition to prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 9, 439-42 (2000)
54. Hsing, A. W., Y. T. Gao, G. Wu, X. Wang, J. Deng, Y. L. Chen, I. A. Sesterhenn, F. K. Mostofi, J. Benichou & C. Chang: Polymorphic CAG and GGN repeat lengths in the androgen receptor gene and prostate cancer risk: a population-based case-control study in China. *Cancer Res*, 60, 5111-6. (2000)
55. Miller, E. A., J. L. Stanford, L. Hsu, E. A. Noonan & E. A. Ostrander: Polymorphic repeats in the androgen receptor gene in high-risk sibships. *Prostate*, 48, 200-205 (2001)
56. Beilin, J., L. Harewood, M. Frydenberg, H. Mameghan, R. F. Martyres, S. J. Farish, C. Yue, D. R. Deam, K. A. Byron & J. D. Zajac: A case-control study of the androgen receptor gene CAG repeat polymorphism in Australian prostate carcinoma subjects. *Cancer*, 92, 941-9. (2001)
57. Latil, A. G., R. Azzouzi, G. S. Cancel, E. C. Guillaume, B. Cochan-Priollet, P. L. Berthon & O. Cussenot: Prostate carcinoma risk and allelic variants of genes involved in androgen biosynthesis and metabolism pathways. *Cancer*, 92, 1130-7. (2001)
58. Modugno, F., J. L. Weissfeld, D. L. Trump, J. M. Zmuda, P. Shea, J. A. Cauley & R. E. Ferrell: Allelic variants of aromatase and the androgen and estrogen receptors: toward a multigenic model of prostate cancer risk. *Clin Cancer Res*, 7, 3092-6. (2001)
59. Mononen, N., T. Ikonen, V. Autio, A. Rokman, M. P. Matikainen, T. L. Tammela, O. P. Kallioniemi, P. A. Koivisto & J. Schleutker: Androgen receptor CAG polymorphism and prostate cancer risk. *Hum Genet*, 111, 166-71. Epub 2002 Jul 3. (2002)
60. Balic, I., S. T. Graham, D. A. Troyer, B. A. Higgins, B. H. Pollock, T. L. Johnson-Pais, I. M. Thompson & R. J. Leach: Androgen receptor length polymorphism associated with prostate cancer risk in Hispanic men. *J Urol*, 168, 2245-8. (2002)
61. Chang, B. L., S. L. Zheng, G. A. Hawkins, S. D. Isaacs, K. E. Wiley, A. Turner, J. D. Carpten, E. R. Bleecker, P. C. Walsh, J. M. Trent, D. A. Meyers, W. B. Isaacs & J. Xu: Polymorphic GGC repeats in the androgen receptor gene are associated with hereditary and sporadic prostate cancer risk. *Hum Genet*, 110, 122-9. Epub 2002 Jan 23. (2002)
62. Chen, C., N. Lamharzi, N. S. Weiss, R. Etzioni, D. A. Dightman, M. Barnett, D. DiTommaso & G. Goodman: Androgen receptor polymorphisms and the incidence of prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 11, 1033-40. (2002)
63. Gsur, A., M. Preyer, G. Haidinger, T. Zidek, S. Madersbacher, G. Schatzl, M. Marberger, C. Vutuc & M. Micksche: Polymorphic CAG repeats in the androgen receptor gene, prostate-specific antigen polymorphism and prostate cancer risk. *Carcinogenesis*, 23, 1647-51. (2002)
64. Huang, S. P., Y. H. Chou, W. S. Chang, M. T. Wu, C. C. Yu, T. Wu, Y. H. Lee, J. K. Huang, W. J. Wu & C. H. Huang: Androgen receptor gene polymorphism and prostate cancer in Taiwan. *J Formos Med Assoc*, 102, 680-6. (2003)
65. Nam, R. K., W. W. Zhang, J. Trachtenberg, M. A. Jewett, M. Emami, D. Vesprini, W. Chu, M. Ho, J. Sweet, A. Evans, A. Toi, M. Pollak & S. A. Narod: Comprehensive assessment of candidate genes and

serological markers for the detection of prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 12, 1429-37. (2003)
66. Santos, M. L., A. S. Sarkis, I. N. Nishimoto & M. A. Nagai: Androgen receptor CAG repeat polymorphism in prostate cancer from a Brazilian population. *Cancer Detect Prev*, 27, 321-6. (2003)
67. Binnie, M. C., F. E. Alexander, C. Heald & F. K. Habib: Polymorphic forms of prostate specific antigen and their interaction with androgen receptor trinucleotide repeats in prostate cancer. *Prostate*, 63, 309-315. (2004)
68. Cicek, M. S., D. V. Conti, A. Curran, P. J. Neville, P. L. Paris, G. Casey & J. S. Witte: Association of prostate cancer risk and aggressiveness to androgen pathway genes: SRD5A2, CYP17, and the AR. *Prostate*, 59, 69-76. (2004)
69. Gilligan, T., J. Manola, O. Sartor, S. P. Weinrich, J. W. Moul & P. W. Kantoff: Absence of a correlation of androgen receptor gene CAG repeat length and prostate cancer risk in an African-American population. *Clin Prostate Cancer*, 3, 98-103. (2004)
70. Forrest, M. S., S. M. Edwards, R. Houlston, Z. Kote-Jarai, T. Key, N. Allen, M. A. Knowles, F. Turner, A. Ardern-Jones, A. Murkin, S. Williams, R. Oram, D. T. Bishop & R. A. Eeles: Association between hormonal genetic polymorphisms and early-onset prostate cancer. *Prostate Cancer Prostatic Dis*, 8, 95-102. (2005)
71. Hayes, V. M., G. Severi, S. A. Eggleton, E. J. Padilla, M. C. Southey, R. L. Sutherland, J. L. Hopper & G. G. Giles: The E211 G>A androgen receptor polymorphism is associated with a decreased risk of metastatic prostate cancer and androgenetic alopecia. *Cancer Epidemiol Biomarkers Prev*, 14, 993-6. (2005)
72. Salinas, C. A., M. A. Austin, E. O. Ostrander & J. L. Stanford: Polymorphisms in the androgen receptor and the prostate-specific antigen genes and prostate cancer risk. *Prostate*, 4, 4 (2005)
73. Mishra, D., K. Thangaraj, A. Mandhani, A. Kumar & R. Mittal: Is reduced CAG repeat length in androgen receptor gene associated with risk of prostate cancer in Indian population? *Clin Genet*, 68, 55-60 (2005)
74. Zeegers, M. P., L. A. Kiemeney, A. M. Nieder & H. Ostrer: How strong is the association between CAG and GGN repeat length polymorphisms in the androgen receptor gene and prostate cancer risk? *Cancer Epidemiol Biomarkers Prev*, 13, 1765-71. (2004)
75. Gruber, S. B., H. Chen, L. P. Tomsho, N. Lee, E. E. Perrone & K. A. Cooney: R726L androgen receptor mutation is uncommon in prostate cancer families in the united states. Prostate, 54, 306-9 (2003)
76. Mononen, N., K. Syrjakoski, M. Matikainen, T. L. Tammela, J. Schleutker, O. P. Kallioniemi, J. Trapman & P. A. Koivisto: Two percent of Finnish prostate cancer patients have a germ-line mutation in the hormone-binding domain of the androgen receptor gene. Cancer Res, 60, 6479-81 (2000)
77. Medeiros, R., A. Vasconcelos, S. Costa, D. Pinto, A. Morais, J. Oliveira & C. Lopees: Steroid hormone genotypes ARStuI and ER325 are linked to the progression of human prostate cancer. Cancer Genet Cytogenet, 141, 91-6 (2003)
78. Hsing, A. W., A. P. Chokkalingam, Y. T. Gao, G. Wu, X. Wang, J. Deng, J. Cheng, I. A. Sesterhenn, F. K. Mostofi, T. Chiang, Y. L. Chen, F. Z. Stanczyk & C. Chang: Polymorphic CAG/CAA repeat length in the AIB1/SRC-3 gene and prostate cancer risk: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev*, 11, 337-41 (2002)
79. Platz, E. A., E. Giovannucci, M. Brown, C. Cieluch, T. F. Shepard, M. J. Stampfer & P. W. Kantoff: Amplified in breast cancer-1 glutamine repeat and prostate cancer risk. *Prostate J*, 2, 27-32 (2000)
80. Carey, A. H., D. Waterworth, K. Patel, D. White, J. Little, P. Novelli, S. Franks & R. Williamson: Polycystic ovaries and premature male pattern baldness are associated with one allele of the steroid metabolism gene CYP17. *Hum Mol Genet*, 3, 1873-6 (1994)
81. Haiman, C. A., S. E. Hankinson, D. Spiegelman, G. A. Colditz, W. C. Willett, F. E. Speizer, K. T. Kelsey & D. J. Hunter: The relationship between a polymorphism in CYP17 with plasma hormone levels and breast cancer. *Cancer Res*, 59, 1015-20 (1999)
82. Lunn, R. M., D. A. Bell, J. L. Mohler & J. A. Taylor: Prostate cancer risk and polymorphism in 17 hydroxylase (CYP17) and steroid reductase (SRD5A2). *Carcinogenesis*, 20, 1727-31. (1999)
83. Wadelius, M., A. O. Andersson, J. E. Johansson, C. Wadelius & E. Rane: Prostate cancer associated with CYP17 genotype. *Pharmacogenetics*, 9, 635-9. (1999)
84. Gsur, A., G. Bernhofer, S. Hinteregger, G. Haidinger, G. Schatzl, S. Madersbacher, M. Marberger, C. Vutuc & M. Micksche: A polymorphism in the CYP17 gene is associated with prostate cancer risk. *Int J Cancer*, 87, 434-7. (2000)
85. Habuchi, T., Z. Liqing, T. Suzuki, R. Sasaki, N. Tsuchiya, H. Tachiki, N. Shimoda, S. Satoh, K. Sato, Y. Kakehi, T. Kamoto, O. Ogawa & T. Kato: Increased risk of prostate cancer and benign prostatic hyperplasia associated with a CYP17 gene polymorphism with a gene dosage effect. *Cancer Res*, 60, 5710-3. (2000)
86. Haiman, C. A., M. J. Stampfer, E. Giovannucci, J. Ma, N. E. Decalo, P. W. Kantoff & D. J. Hunter: The relationship between a polymorphism in CYP17 with plasma hormone levels and prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 10, 743-8. (2001)
87. Yamada, Y., M. Watanabe, M. Murata, M. Yamanaka, Y. Kubota, H. Ito, T. Katoh, J. Kawamura, R. Yatani & T. Shiraishi: Impact of genetic polymorphisms of 17-hydroxylase cytochrome P-450 (CYP17) and steroid 5alpha-reductase type II (SRD5A2) genes on prostate-cancer risk among the Japanese population. *Int J Cancer*, 92, 683-6. (2001)
88. Kittles, R. A., R. K. Panguluri, W. Chen, A. Massac, C. Ahaghotu, A. Jackson, F. Ukoli, L. Adams-Campbell, W. Isaacs & G. M. Dunston: Cyp17 promoter variant associated with prostate cancer aggressiveness in African Americans. Cancer Epidemiol Biomarkers Prev, 10, 943-7. (2001)
89. Chang, B., S. L. Zheng, S. D. Isaacs, K. E. Wiley, J. D. Carpten, G. A. Hawkins, E. R. Bleecker, P. C. Walsh, J. M. Trent, D. A. Meyers, W. B. Isaacs & J. Xu: Linkage and association of CYP17 gene in hereditary and sporadic prostate cancer. Int J Cancer, 95, 354-9. (2001)
90. Stanford, J. L., E. A. Noonan, L. Iwasaki, S. Kolb, R. B. Chadwick, Z. Feng & E. A. Ostrander: A polymorphism in the CYP17 gene and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 11, 243-7. (2002)
91. Madigan, M. P., Y. T. Gao, J. Deng, R. M. Pfeiffer, B. L. Chang, S. Zheng, D. A. Meyers, F. Z. Stanczyk, J. Xu &

A. W. Hsing: CYP17 polymorphisms in relation to risks of prostate cancer and benign prostatic hyperplasia: a population-based study in China. *Int J Cancer*, 107, 271-5. (2003)
92. Lin, C. C., H. C. Wu, W. C. Chen, H. Y. Chen & F. J. Tsai: CYP17 gene promoter allelic variant is not associated with prostate cancer. *Urol Oncol*, 21, 262-5. (2003)
93. Antognelli, C., L. Mearini, V. N. Talesa, A. Giannantoni & E. Mearini: Association of CYP17, GSTP1, and PON1 polymorphisms with the risk of prostate cancer. *Prostate*, 63, 240-51. (2005)
94. Ntais, C., A. Polycarpou & J. P. Ioannidis: Association of the CYP17 gene polymorphism with the risk of prostate cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 12, 120-6. (2003)
95. Allen, N. E., M. S. Forrest & T. J. Key: The association between polymorphisms in the CYP17 and 5alpha-reductase (SRD5A2) genes and serum androgen concentrations in men. *Cancer Epidemiol Biomarkers Prev*, 10, 185-9 (2001)
96. Suzuki, K., H. Nakazato, H. Matsui, H. Koike, H. Okugi, N. Ohtake, T. Takei, S. Nakata, M. Hasumi & H. Yamanaka: Association of the genetic polymorphism of the CYP19 intron 4[TTTA]n repeat with familial prostate cancer risk in a Japanese population. *Anticancer Res*, 23, 4941-6. (2003)
97. Fukatsu, T., Y. Hirokawa, T. Araki, T. Hioki, T. Murata, H. Suzuki, T. Ichikawa, H. Tsukino, D. Qiu, T. Katoh, Y. Sugimura, R. Yatani, T. Shiraishi & M. Watanabe: Genetic polymorphisms of hormone-related genes and prostate cancer risk in the Japanese population. *Anticancer Res*, 24, 2431-7. (2004)
98. Li, L., M. S. Cicek, G. Casey & J. S. Witte: No association between a tetranucleotide repeat polymorphism of CYP19 and prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 13, 2280-1. (2004)
99. Ross, R. K., L. Bernstein, R. A. Lobo, H. Shimizu, F. Z. Stanczyk, M. C. Pike & B. E. Henderson: 5-alpha-reductase activity and risk of prostate cancer among Japanese and US white and black males. *Lancet*, 339, 887-9 (1992)
100. Lookingbill, D. P., L. M. Demers, C. Wang, A. Leung, R. S. Rittmaster & R. J. Santen: Clinical and biochemical parameters of androgen action in normal healthy Caucasian versus Chinese subjects. *J Clin Endocrinol Metab*, 72, 1242-8 (1991)
101. Makridakis, N. M., E. di Salle & J. K. Reichardt: Biochemical and pharmacogenetic dissection of human steroid 5 alpha-reductase type II. *Pharmacogenetics*, 10, 407-13 (2000)
102. Kantoff, P. W., P. G. Febbo, E. Giovannucci, K. Krithivas, D. M. Dahl, G. Chang, C. H. Hennekens, M. Brown & M. J. Stampfer: A polymorphism of the 5 alpha-reductase gene and its association with prostate cancer: a case-control analysis. *Cancer Epidemiol Biomarkers Prev*, 6, 189-92. (1997)
103. Febbo, P. G., P. W. Kantoff, E. A. Platz, D. Casey, S. Batter, E. Giovannucci, C. H. Hennekens & M. J. Stampfer: The V89L polymorphism in the 5alpha-reductase type 2 gene and risk of prostate cancer. *Cancer Res*, 59, 5878-81. (1999)
104. Makridakis, N. M., R. K. Ross, M. C. Pike, L. E. Crocitto, L. N. Kolonel, C. L. Pearce, B. E. Henderson & J. K. Reichardt: Association of mis-sense substitution in SRD5A2 gene with prostate cancer in African-American and Hispanic men in Los Angeles, USA. *Lancet*, 354, 975-8. (1999)
105. Margiotti, K., F. Sangiuolo, A. De Luca, F. Froio, C. L. Pearce, V. Ricci-Barbini, F. Micali, M. Bonafe, C. Franceschi, B. Dallapiccola, G. Novelli & J. K. Reichardt: Evidence for an association between the SRD5A2 (type II steroid 5 alpha-reductase) locus and prostate cancer in Italian patients. *Dis Markers*, 16, 147-50. (2000)
106. Nam, R. K., A. Toi, D. Vesprini, M. Ho, W. Chu, S. Harvie, J. Sweet, J. Trachtenberg, M. A. Jewett & S. A. Narod: V89L polymorphism of type-2, 5-alpha reductase enzyme gene predicts prostate cancer presence and progression. *Urology*, 57, 199-204. (2001)
107. Mononen, N., T. Ikonen, K. Syrjakoski, M. P. Matikainen, J. Schleutker, T. L. Tammela, P. A. Koivisto & O. P. Kallioniemi: A missense substitution A49T in the steroid 5-alpha-reductase gene (SRD5A2) is not associated with prostate cancer in Finland. *Br J Cancer*, 84, 1344-1347 (2001)
108. Hsing, A. W., C. Chen, A. P. Chokkalingam, Y. T. Gao, D. A. Dightman, H. T. Nguyen, J. Deng, J. Cheng, I. A. Sesterhenn, F. K. Mostofi, F. Z. Stanczyk & J. K. Reichardt: Polymorphic markers in the SRD5A2 gene and prostate cancer risk: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev*, 10, 1077-82. (2001)
109. Pearce, C. L., N. M. Makridakis, R. K. Ross, M. C. Pike, L. N. Kolonel, B. E. Henderson & J. K. Reichardt: Steroid 5-alpha reductase type II V89L substitution is not associated with risk of prostate cancer in a multiethnic population study. *Cancer Epidemiol Biomarkers Prev*, 11, 417-8. (2002)
110. Soderstrom, T., M. Wadelius, S. O. Andersson, J. E. Johansson, S. Johansson, F. Granath & A. Rane: 5alpha-reductase 2 polymorphisms as risk factors in prostate cancer. *Pharmacogenetics*, 12, 307-12. (2002)
111. Lamharzi, N., M. M. Johnson, G. Goodman, R. Etzioni, N. S. Weiss, D. A. Dightman, M. Barnett, D. DiTommaso & C. Chen: Polymorphic markers in the 5alpha-reductase type II gene and the incidence of prostate cancer. *Int J Cancer*, 105, 480-3. (2003)
112. Chang, B. L., S. L. Zheng, S. D. Isaacs, A. R. Turner, E. R. Bleecker, P. C. Walsh, D. A. Meyers, W. B. Isaacs & J. Xu: Evaluation of SRD5A2 sequence variants in susceptibility to hereditary and sporadic prostate cancer. *Prostate*, 56, 37-44. (2003)
113. Li, Z., T. Habuchi, K. Mitsumori, T. Kamoto, H. Kinoshitu, T. Segawa, O. Ogawa & T. Kato: Association of V89L SRD5A2 polymorphism with prostate cancer development in a Japanese population. *J Urol*, 169, 2378-81. (2003)
114. Jaffe, J. M., S. B. Malkowicz, A. H. Walker, S. MacBride, R. Peschel, J. Tomaszewski, K. Van Arsdalen, A. J. Wein & T. R. Rebbeck: Association of SRD5A2 genotype and pathological characteristics of prostate tumors. *Cancer Res*, 60, 1626-30 (2000)
115. Ntais, C., A. Polycarpou & J. P. Ioannidis: SRD5A2 gene polymorphisms and the risk of prostate cancer: a

meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 12, 618-24. (2003)
116. Margiotti, K., E. Kim, C. L. Pearce, E. Spera, G. Novelli & J. K. Reichardt: Association of the G289S single nucleotide polymorphism in the HSD17B3 gene with prostate cancer in Italian men. *Prostate*, 53, 65-8. (2002)
117. Chang, B. L., S. L. Zheng, G. A. Hawkins, S. D. Isaacs, K. E. Wiley, A. Turner, J. D. Carpten, E. R. Bleecker, P. C. Walsh, J. M. Trent, D. A. Meyers, W. B. Isaacs & J. Xu: Joint effect of HSD3B1 and HSD3B2 genes is associated with hereditary and sporadic prostate cancer susceptibility. *Cancer Res*, 62, 1784-9. (2002)
118. Kraft, P., P. Pharoah, S. J. Chanock, D. Albanes, L. N. Kolonel, R. B. Hayes, D. Altshuler, G. Andriole, C. Berg, H. Boeing, N. P. Burtt, B. Bueno-de-Mesquita, E. E. Calle, H. Cann, F. Canzian, Y. C. Chen, D. E. Crawford, A. M. Dunning, H. S. Feigelson, M. L. Freedman, J. M. Gaziano, E. Giovannucci, C. A. Gonzalez, C. A. Haiman, G. Hallmans, B. E. Henderson, J. N. Hirschhorn, D. J. Hunter, R. Kaaks, T. Key, L. L. Marchand, J. Ma, K. Overvad, D. Palli, M. C. Pike, E. Riboli, C. Rodriguez, W. V. Setiawan, M. J. Stampfer, D. O. Stram, G. Thomas, M. J. Thun, R. Travis, A. Trichopoulou, J. Virtamo & S. Wacholder: Genetic Variation in the HSD17B1 Gene and Risk of Prostate Cancer. *PLoS Genet*, 1, e68 (2005)
119. Rebbeck, T. R., J. M. Jaffe, A. H. Walker, A. J. Wein & S. B. Malkowicz: Modification of clinical presentation of prostate tumors by a novel genetic variant in CYP3A4. *J Natl Cancer Inst*, 90, 1225-9. (1998)
120. Zeigler-Johnson, C. M., A. H. Walker, B. Mancke, E. Spangler, M. Jalloh, S. McBride, A. Deitz, S. B. Malkowicz, D. Ofori-Adjei, S. M. Gueye & T. R. Rebbeck: Ethnic differences in the frequency of prostate cancer susceptibility alleles at SRD5A2 and CYP3A4. *Hum Hered*, 54, 13-21 (2002)
121. Bangsi, D., J. Zhou, Y. Sun, N. P. Patel, L. L. Darga, L. K. Heilbrun, I. J. Powell, R. K. Severson & R. B. Everson: Impact of a genetic variant in CYP3A4 on risk and clinical presentation of prostate cancer among white and African-American men. *Urol Oncol*, 24, 21-7 (2006)
122. Plummer, S. J., D. V. Conti, P. L. Paris, A. P. Curran, G. Casey & J. S. Witte: CYP3A4 and CYP3A5 genotypes, haplotypes, and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 12, 928-32 (2003)
123. Zeigler-Johnson, C., T. Friebel, A. H. Walker, Y. Wang, E. Spangler, S. Panossian, M. Patacsil, R. Aplenc, A. J. Wein, S. B. Malkowicz & T. R. Rebbeck: CYP3A4, CYP3A5, and CYP3A43 genotypes and haplotypes in the etiology and severity of prostate cancer. *Cancer Res*, 64, 8461-7. (2004)
124. Zhenhua, L., N. Tsuchiya, S. Narita, T. Inoue, Y. Horikawa, H. Kakinuma, T. Kato, O. Ogawa & T. Habuchi: CYP3A5 gene polymorphism and risk of prostate cancer in a Japanese population. *Cancer Lett*, 225, 237-43 (2005)
125. Kuehl, P., J. Zhang, Y. Lin, J. Lamba, M. Assem, J. Schuetz, P. B. Watkins, A. Daly, S. A. Wrighton, S. D. Hall, P. Maurel, M. Relling, C. Brimer, K. Yasuda, R. Venkataramanan, S. Strom, K. Thummel, M. S. Boguski & E. Schuetz: Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet*, 27, 383-91 (2001)
126. Farnsworth, W. E.: Estrogen in the etiopathogenesis of BPH. *Prostate*, 41, 263-74 (1999)
127. Gupta, C.: The role of estrogen receptor, androgen receptor and growth factors in diethylstilbestrol-induced programming of prostate differentiation. *Urol Res*, 28, 223-9 (2000)
128. Shirai, T., M. Sano, K. Imaida, S. Takahashi, T. Mori & N. Ito: Duration dependent induction of invasive prostatic carcinomas with pharmacological dose of testosterone propionate in rats pretreated with 3,2'-dimethyl-4-aminobiphenyl and development of androgen-independent carcinomas after castration. *Cancer Lett*, 83, 111-6 (1994)
129. Bosland, M. C., H. Ford & L. Horton: Induction at high incidence of ductal prostate adenocarcinomas in NBL/Cr and Sprague-Dawley Hsd:SD rats treated with a combination of testosterone and estradiol-17 beta or diethylstilbestrol. *Carcinogenesis*, 16, 1311-7 (1995)
130. Strohsnitter, W. C., K. L. Noller, R. N. Hoover, S. J. Robboy, J. R. Palmer, L. Titus-Ernstoff, R. H. Kaufman, E. Adam, A. L. Herbst & E. E. Hatch: Cancer risk in men exposed in utero to diethylstilbestrol. *J Natl Cancer Inst*, 93, 545-51 (2001)
131. Lau, K. M., M. LaSpina, J. Long & S. M. Ho: Expression of estrogen receptor (ER)-alpha and ER-beta in normal and malignant prostatic epithelial cells: regulation by methylation and involvement in growth regulation. *Cancer Res*, 60, 3175-82 (2000)
132. Gustafsson, J. A.: An update on estrogen receptors. *Semin Perinatol*, 24, 66-9 (2000)
133. Srinivasan, G., E. Campbell & N. Bashirelahi: Androgen, estrogen, and progesterone receptors in normal and aging prostates. *Microsc Res Tech*, 30, 293-304 (1995)
134. Weihua, Z., S. Makela, L. C. Andersson, S. Salmi, S. Saji, J. I. Webster, E. V. Jensen, S. Nilsson, M. Warner & J. A. Gustafsson: A role for estrogen receptor beta in the regulation of growth of the ventral prostate. *Proc Natl Acad Sci U S A*, 98, 6330-5 (2001)
135. Rosner, W., D. J. Hryb, M. S. Khan, A. M. Nakhla & N. A. Romas: Sex hormone-binding globulin mediates steroid hormone signal transduction at the plasma membrane. *J Steroid Biochem Mol Biol*, 69, 481-5 (1999)
136. Nakhla, A. M., N. A. Romas & W. Rosner: Estradiol activates the prostate androgen receptor and prostate-specific antigen secretion through the intermediacy of sex hormone-binding globulin. *J Biol Chem*, 272, 6838-41 (1997)
137. Farnsworth, W. E.: Roles of estrogen and SHBG in prostate physiology. *Prostate*, 28, 17-23 (1996)
138. Fortunati, N., M. Becchis, M. G. Catalano, A. Comba, P. Ferrera, M. Raineri, L. Berta & R. Frairia: Sex hormone-binding globulin, its membrane receptor, and breast cancer: a new approach to the modulation of estradiol action in neoplastic cells. *J Steroid Biochem Mol Biol*, 69, 473-9 (1999)
139. Plymate, S. R., S. M. Loop, R. C. Hoop, K. M. Wiren, R. Ostenson, D. J. Hryb & W. Rosner: Effects of sex hormone binding globulin (SHBG) on human prostatic carcinoma. *J Steroid Biochem Mol Biol*, 40, 833-9 (1991)
140. Peiris, A. N., J. I. Stagner, S. R. Plymate, R. L. Vogel, M. Heck & E. Samols: Relationship of insulin secretory

pulses to sex hormone-binding globulin in normal men. *J Clin Endocrinol Metab*, 76, 279-82 (1993)
141. Hsing, A. W., J. Deng, I. A. Sesterhenn, F. K. Mostofi, F. Z. Stanczyk, J. Benichou, T. Xie & Y. T. Gao: Body size and prostate cancer: a population-based case-control study in China. *Cancer Epidemiol Biomarkers Prev*, 9, 1335-41. (2000)
142. Nomura, A. M.: Body size and prostate cancer. *Epidemiol Rev*, 23, 126-31 (2001)
143. Lagiou, P., L. B. Signorello, D. Trichopoulos, A. Tzonou, A. Trichopoulou & C. S. Mantzoros: Leptin in relation to prostate cancer and benign prostatic hyperplasia. *Int J Cancer*, 76, 25-8 (1998)
144. Hsing, A. W., S. Chua, Jr., Y. T. Gao, E. Gentzschein, L. Chang, J. Deng & F. Z. Stanczyk: Prostate cancer risk and serum levels of insulin and leptin: a population-based study. *J Natl Cancer Inst*, 93, 783-9. (2001)
145. Stattin, P., S. Soderberg, G. Hallmans, A. Bylund, R. Kaaks, U. H. Stenman, A. Bergh & T. Olsson: Leptin is associated with increased prostate cancer risk: a nested case-referent study. *J Clin Endocrinol Metab*, 86, 1341-5 (2001)
146. Chang, S., S. D. Hursting, J. H. Contois, S. S. Strom, Y. Yamamura, R. J. Babaian, P. Troncoso, P. S. Scardino, T. M. Wheeler, C. I. Amos & M. R. Spitz: Leptin and prostate cancer. *Prostate*, 46, 62-7. (2001)
147. Giovannucci, E., E. B. Rimm, Y. Liu & W. C. Willett: Height, predictors of C-peptide and cancer risk in men. *Int J Epidemiol*, 33, 217-25 (2004)
148. Solano, D. C., M. Sironi, C. Bonfini, S. B. Solerte, S. Govoni & M. Racchi: Insulin regulates soluble amyloid precursor protein release via phosphatidyl inositol 3 kinase-dependent pathway. *Faseb J*, 14, 1015-22 (2000)
149. Prisco, M., G. Romano, F. Peruzzi, B. Valentinis & R. Baserga: Insulin and IGF-I receptors signaling in protection from apoptosis. *Horm Metab Res*, 31, 80-9 (1999)
150. Christoffersen, C. T., H. Tornqvist, C. J. Vlahos, D. Bucchini, J. Jami, P. De Meyts & R. L. Joshi: Insulin and insulin-like growth factor-I receptor mediated differentiation of 3T3-F442A cells into adipocytes: effect of PI 3-kinase inhibition. *Biochem Biophys Res Commun*, 246, 426-30 (1998)
151. Qin, K. N. & R. L. Rosenfield: Role of cytochrome P450c17 in polycystic ovary syndrome. *Mol Cell Endocrinol*, 145, 111-21 (1998)
152. Pasquali, R., F. Casimirri, R. De Iasio, P. Mesini, S. Boschi, R. Chierici, R. Flamia, M. Biscotti & V. Vicennati: Insulin regulates testosterone and sex hormone-binding globulin concentrations in adult normal weight and obese men. *J Clin Endocrinol Metab*, 80, 654-8 (1995)
153. Nestler, J. E.: Regulation of the aromatase activity of human placental cytotrophoblasts by insulin, insulin-like growth factor-I, and -II. *J Steroid Biochem Mol Biol*, 44, 449-57 (1993)
154. Bhatia, B. & C. A. Price: Insulin alters the effects of follicle stimulating hormone on aromatase in bovine granulosa cells in vitro. *Steroids*, 66, 511-9 (2001)
155. Moule, S. K. & R. M. Denton: Multiple signaling pathways involved in the metabolic effects of insulin. *Am J Cardiol*, 80, 41A-49A (1997)
156. Yu, H. & T. Rohan: Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst*, 92, 1472-89. (2000)
157. Ho, G. Y., A. Melman, S. M. Liu, M. Li, H. Yu, A. Negassa, R. D. Burk, A. W. Hsing, R. Ghavamian & S. C. Chua, Jr.: Polymorphism of the insulin gene is associated with increased prostate cancer risk. *Br J Cancer*, 88, 263-9. (2003)
158. Claeys, G. B., A. V. Sarma, R. L. Dunn, K. A. Zuhlke, J. Beebe-Dimmer, J. E. Montie, K. J. Wojno, D. Schottenfeld & K. A. Cooney: INSPstI polymorphism and prostate cancer in African-American men. *Prostate*, 2, 2 (2005)
159. Neuhausen, S. L., M. L. Slattery, C. P. Garner, Y. C. Ding, M. Hoffman & A. R. Brothman: Prostate cancer risk and IRS1, IRS2, IGF1, and INS polymorphisms: Strong association of IRS1 G972R variant and cancer risk. *Prostate*, 64, 168-74. (2005)
160. Li, L., M. S. Cicek, G. Casey & J. S. Witte: No association between genetic polymorphisms in insulin and insulin receptor substrate-1 and prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 14, 2462-3 (2005)
161. Ribeiro, R., A. Vasconcelos, S. Costa, D. Pinto, A. Morais, J. Oliveira, F. Lobo, C. Lopes & R. Medeiros: Overexpressing leptin genetic polymorphism (-2548 G/A) is associated with susceptibility to prostate cancer and risk of advanced disease. *Prostate*, 59, 268-74 (2004)
162. Kote-Jarai, Z., R. Singh, F. Durocher, D. Easton, S. M. Edwards, A. Ardern-Jones, D. P. Dearnaley, R. Houlston, R. Kirby & R. Eeles: Association between leptin receptor gene polymorphisms and early-onset prostate cancer. *BJU Int*, 92, 109-12 (2003)
163. Chan, J. M., M. J. Stampfer, J. Ma, P. Gann, J. M. Gaziano, M. Pollak & E. Giovannucci: Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 as predictors of advanced-stage prostate cancer. *J Natl Cancer Inst*, 94, 1099-106 (2002)
164. LeRoith, D. & C. T. Roberts, Jr.: The insulin-like growth factor system and cancer. Cancer Lett, 195, 127-37. (2003)
165. Woodson, K., J. A. Tangrea, M. Pollak, T. D. Copeland, P. R. Taylor, J. Virtamo & D. Albanes: Serum insulin-like growth factor I: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. *Cancer Res*, 63, 3991-4 (2003)
166. Stattin, P., S. Rinaldi, C. Biessy, U. H. Stenman, G. Hallmans & R. Kaaks: High levels of circulating insulin-like growth factor-I increase prostate cancer risk: a prospective study in a population-based nonscreened cohort. *J Clin Oncol*, 22, 3104-12. (2004)
167. Chen, C., S. K. Lewis, L. Voigt, A. Fitzpatrick, S. R. Plymate & N. S. Weiss: Prostate carcinoma incidence in relation to prediagnostic circulating levels of insulin-like growth factor I, insulin-like growth factor binding protein 3, and insulin. *Cancer*, 103, 76-84. (2005)
168. Chokkalingam, A. P., M. Pollak, C. M. Fillmore, Y. T. Gao, F. Z. Stanczyk, J. Deng, I. A. Sesterhenn, F. K. Mostofi, T. R. Fears, M. P. Madigan, R. G. Ziegler, J. F. Fraumeni, Jr. & A. W. Hsing: Insulin-like growth factors and prostate cancer: a population-based case-control study in China. *Cancer Epidemiol Biomarkers Pre*v, 10, 421-7 (2001)
169. Friedrichsen, D. M., S. Hawley, J. Shu, M. Humphrey, L. Sabacan, L. Iwasaki, R. Etzioni, E. A. Ostrander & J. L. Stanford: IGF-I and IGFBP-3 polymorphisms and risk of prostate cancer. *Prostate*, 30, 30 (2005)
170. Schildkraut, J. M., W. Demark-Wahnefried, R. M. Wenham, J. Grubber, A. S. Jeffreys, S. C. Grambow, J. R. Marks, P. G. Moorman, C. Hoyo, S. Ali & P. J. Walther: IGF1

(CA)19 repeat and IGFBP3 -202 A/C genotypes and the risk of prostate cancer in Black and White men. Cancer Epidemiol *Biomarkers Prev*, 14, 403-8. (2005)
171. Tsuchiya, N., L. Wang, Y. Horikawa, T. Inoue, H. Kakinuma, S. Matsuura, K. Sato, O. Ogawa, T. Kato & T. Habuchi: CA repeat polymorphism in the insulin-like growth factor-I gene is associated with increased risk of prostate cancer and benign prostatic hyperplasia. *Int J Oncol,* 26, 225-31. (2005)
172. Li, L., M. S. Cicek, G. Casey & J. S. Witte: No association between genetic polymorphisms in IGF-I and IGFBP-3 and prostate cancer. Cancer Epidemio*l Biomarkers Prev*, 13, 497-8. (2004)
173. Lai, M. T., R. H. Chen, F. J. Tsai, L. Wan & W. C. Chen: Glutathione S-transferase M1 gene but not insulin-like growth factor-2 gene or epidermal growth factor gene is associated with prostate cancer. *Urol Onco*l, 23, 225-9 (2005)
174. Wang, L., T. Habuchi, N. Tsuchiya, K. Mitsumori, C. Ohyama, K. Sato, H. Kinoshita, T. Kamoto, A. Nakamura, O. Ogawa & T. Kato: Insulin-like growth factor-binding protein-3 gene -202 A/C polymorphism is correlated with advanced disease status in prostate cancer. *Cancer Res*, 63, 4407-11. (2003)
175. Blutt, S. E. & N. L. Weigel: Vitamin D and prostate cancer. Proc Soc Exp Biol Med, 221, 89-98 (1999)
176. Getzenberg, R. H., B. W. Light, P. E. Lapco, B. R. Konety, A. K. Nangia, J. S. Acierno, R. Dhir, Z. Shurin, R. S. Day, D. L. Trump & C. S. Johnson: Vitamin D inhibition of prostate adenocarcinoma growth and metastasis in the Dunning rat prostate model syste*m. Urology*, 50, 999-1006 (1997)
177. Beer, T. M.: ASCENT: the androgen-independent prostate cancer study of calcitriol enhancing taxotere. *BJU Int,* 96, 508-13 (2005)
178. Taylor, J. A., A. Hirvonen, M. Watson, G. Pittman, J. L. Mohler & D. A. Bell: Association of prostate cancer with vitamin D receptor gene polymorphism. *Cancer Res,* 56, 4108-10. (1996)
179. Ingles, S. A., G. A. Coetzee, R. K. Ross, B. E. Henderson, L. N. Kolonel, L. Crocitto, W. Wang & R. W. Haile: Association of prostate cancer with vitamin D receptor haplotypes in African-Americans. *Cancer Res,* 58, 1620-3. (1998)
180. Ma, J., M. J. Stampfer, P. H. Gann, H. L. Hough, E. Giovannucci, K. T. Kelsey, C. H. Hennekens & D. J. Hunter: Vitamin D receptor polymorphisms, circulating vitamin D metabolites, and risk of prostate cancer in United States physicians. *Cancer Epidemiol Biomarkers Prev,* 7, 385-90. (1998)
181. Correa-Cerro, L., P. Berthon, J. Haussler, S. Bochum, E. Drelon, P. Mangin, G. Fournier, T. Paiss, O. Cussenot & W. Vogel: Vitamin D receptor polymorphisms as markers in prostate cance*r. Hum Genet,* 105, 281-7. (1999)
182. Furuya, Y., K. Akakura, M. Masai & H. Ito: Vitamin D receptor gene polymorphism in Japanese patients with prostate cancer. *Endocr J*, 46, 467-70. (1999)
183. Watanabe, M., K. Fukutome, M. Murata, H. Uemura, Y. Kubota, J. Kawamura & R. Yatani: Significance of vitamin D receptor gene polymorphism for prostate cancer risk in Japanese. *Anticancer Res*, 19, 4511-4. (1999)
184. Habuchi, T., T. Suzuki, R. Sasaki, L. Wang, K. Sato, S. Satoh, T. Akao, N. Tsuchiya, N. Shimoda, Y. Wada, A. Koizumi, J. Chihara, O. Ogawa & T. Kato: Association of vitamin D receptor gene polymorphism with prostate cancer and benign prostatic hyperplasia in a Japanese population. *Cancer Res*, 60, 305-8. (2000)
185. Blazer, D. G., 3rd, D. M. Umbach, R. M. Bostick & J. A. Taylor: Vitamin D receptor polymorphisms and prostate cancer. *Mol Carcinog*, 27, 18-23. (2000)
186. Chokkalingam, A. P., K. A. McGlynn, Y. T. Gao, M. Pollak, J. Deng, I. A. Sesterhenn, F. K. Mostofi, J. F. Fraumeni, Jr. & A. W. Hsing: Vitamin D receptor gene polymorphisms, insulin-like growth factors, and prostate cancer risk: a population-based case-control study in China. *Cancer Res*, 61, 4333-6. (2001)
187. Gsur, A., S. Madersbacher, G. Haidinger, G. Schatzl, M. Marberger, C. Vutuc & M. Micksche: Vitamin D receptor gene polymorphism and prostate cancer risk. *Prostate*, 51, 30-4. (2002)
188. Hamasaki, T., H. Inatomi, T. Katoh, T. Ikuyama & T. Matsumoto: Significance of vitamin D receptor gene polymorphism for risk and disease severity of prostate cancer and benign prostatic hyperplasia in Japanese. *Urol Int*, 68, 226-31. (2002)
189. Medeiros, R., A. Morais, A. Vasconcelos, S. Costa, D. Pinto, J. Oliveira & C. Lopes: The role of vitamin D receptor gene polymorphisms in the susceptibility to prostate cancer of a southern European population. *J Hum Genet*, 47, 413-8. (2002)
190. Suzuki, K., H. Matsui, N. Ohtake, S. Nakata, T. Takei, H. Koike, H. Nakazato, H. Okugi, M. Hasumi, Y. Fukabori, K. Kurokawa & H. Yamanaka: Vitamin D receptor gene polymorphism in familial prostate cancer in a Japanese population. *Int J Urol*, 10, 261-6. (2003)
191. Maistro, S., I. Snitcovsky, A. S. Sarkis, I. A. da Silva & M. M. Brentani: Vitamin D receptor polymorphisms and prostate cancer risk in Brazilian men. *Int J Biol Markers*, 19, 245-9. (2004)
192. Oakley-Girvan, I., D. Feldman, T. R. Eccleshall, R. P. Gallagher, A. H. Wu, L. N. Kolonel, J. Halpern, R. R. Balise, D. W. West, R. S. Paffenbarger, Jr. & A. S. Whittemore: Risk of early-onset prostate cancer in relation to germ line polymorphisms of the vitamin D receptor. *Cancer Epidemiol Biomarkers Prev*, 13, 1325-30. (2004)
193. Cheteri, M. B., J. L. Stanford, D. M. Friedrichsen, M. A. Peters, L. Iwasaki, M. C. Langlois, Z. Feng & E. A. Ostrander: Vitamin D receptor gene polymorphisms and prostate cancer risk. *Prostate*, 59, 409-18. (2004)
194. Huang, S. P., Y. H. Chou, W. S. Wayne Chang, M. T. Wu, Y. Y. Chen, C. C. Yu, T. T. Wu, Y. H. Lee, J. K. Huang, W. J. Wu & C. H. Huang: Association between vitamin D receptor polymorphisms and prostate cancer risk in a Taiwanese population. *Cancer Lett*, 207, 69-77. (2004)
195. Mishra, D. K., H. K. Bid, D. S. Srivastava, A. Mandhani & R. D. Mittal: Association of vitamin D receptor gene polymorphism and risk of prostate cancer in India. *Urol Int*, 74, 315-8. (2005)
196. Hayes, V. M., G. Severi, E. J. Padilla, S. A. Eggleton, M. C. Southey, R. L. Sutherland, J. L. Hopper & G. G. Giles: Genetic variants in the vitamin D receptor gene and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev*, 14, 997-9. (2005)
197. Ntais, C., A. Polycarpou & J. P. Ioannidis: Vitamin D receptor gene polymorphisms and risk of prostate cancer: a

meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 12, 1395-402. (2003)
198. Farnsworth, W. E., W. R. Slaunwhite, Jr., M. Sharma, F. Oseko, J. R. Brown, M. J. Gonder & R. Cartagena: Interaction of prolactin and testosterone in the human prostate. *Urol Res*, 9, 79-88 (1981)
199. Stattin, P., S. Rinaldi, U. H. Stenman, E. Riboli, G. Hallmans, A. Bergh & R. Kaaks: Plasma prolactin and prostate cancer risk: A prospective study. *Int J Cancer*, 92, 463-5 (2001)
200. Henderson, B. E., L. Bernstein, R. K. Ross, R. H. Depue & H. L. Judd: The early in utero oestrogen and testosterone environment of blacks and whites: potential effects on male offspring. *Br J Cancer*, 57, 216-8 (1988)
201. Wacholder, S., S. Chanock, M. Garcia-Closas, L. El Ghormli & N. Rothman: Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. *J Natl Cancer Inst*, 96, 434-42 (2004)
202. Ioannidis, J. P., M. Gwinn, J. Little, J. P. Higgins, J. L. Bernstein, P. Boffetta, M. Bondy, M. S. Bray, P. E. Brenchley, P. A. Buffler, J. P. Casas, A. P. Chokkalingam, J. Danesh, G. Davey-Smith, S. Dolan, R. Duncan, N. A. Gruis, P. Hartge, M. Hashibe, D. J. Hunter, M.-R. Jarvelin, B. Malmer, D. M. Maraganore, J. A. Newton-Bishop, T. R. O'Brien, G. Petersen, E. Riboli, G. Salanti, D. Seminara, L. Smeeth, E. Taioli, N. Timpson, A. G. Uitterlinden, P. Vineis, N. Wareham, D. M. Winn, R. Zimmern & M. J. Khoury: A road map for efficient and reliable human genome epidemiology. *Nat Genet*, 38, 3-5 (2006)
203. Morton, L. M., T. Zheng, T. R. Holford, E. A. Holly, B. C. Chiu, A. S. Costantini, E. Stagnaro, E. V. Willett, L. Dal Maso, D. Serraino, E. T. Chang, W. Cozen, S. Davis, R. K. Severson, L. Bernstein, S. T. Mayne, F. R. Dee, J. R. Cerhan & P. Hartge: Alcohol consumption and risk of non-Hodgkin lymphoma: a pooled analysis. *Lancet Oncol*, 6, 469-76 (2005)
204. Wacholder, S., N. Rothman & N. Caporaso: Counterpoint: bias from population stratification is not a major threat to the validity of conclusions from epidemiological studies of common polymorphisms and cancer. *Cancer Epidemiol Biomarkers Prev*, 11, 513-20 (2002)
205. Yang, N., H. Li, L. A. Criswell, P. K. Gregersen, M. E. Alarcon-Riquelme, R. Kittles, R. Shigeta, G. Silva, P. I. Patel, J. W. Belmont & M. F. Seldin: Examination of ancestry and ethnic affiliation using highly informative diallelic DNA markers: application to diverse and admixed populations and implications for clinical epidemiology and forensic medicine. *Hum Genet*, 118, 382-92 (2005)
206. http://genmapp.org., Gladstone Institute, University of California, San Francisco
207. Hung, R. J., P. Brennan, C. Malaveille, S. Porru, F. Donato, P. Boffetta & J. S. Witte: Using hierarchical modeling in genetic association studies with multiple markers: application to a case-control study of bladder cancer. *Cancer Epidemiol Biomarkers Prev*, 13, 1013-21 (2004)
208. Hahn, L. W., M. D. Ritchie & J. H. Moore: Multifactor dimensionality reduction software for detecting gene-gene and gene-environment interactions. *Bioinformatics*, 19, 376-82 (2003)
209. Hayes, R. B.: Gene-environment interrelations in prostate cancer. *Epidemiol Rev*, 23, 163-7 (2001)
210. Hunter, D. J., E. Riboli, C. A. Haiman, D. Albanes, D. Altshuler, S. J. Chanock, R. B. Haynes, B. E. Henderson, R. Kaaks, D. O. Stram, G. Thomas, M. J. Thun, H. Blanche, J. E. Buring, N. P. Burtt, E. E. Calle, H. Cann, F. Canzian, Y. C. Chen, G. A. Colditz, D. G. Cox, A. M. Dunning, H. S. Feigelson, M. L. Freedman, J. M. Gaziano, E. Giovannucci, S. E. Hankinson, J. N. Hirschhorn, R. N. Hoover, T. Key, L. N. Kolonel, P. Kraft, L. Le Marchand, S. Liu, J. Ma, S. Melnick, P. Pharaoh, M. C. Pike, C. Rodriguez, V. W. Setiawan, M. J. Stampfer, E. Trapido, R. Travis, J. Virtamo, S. Wacholder & W. C. Willett: A candidate gene approach to searching for low-penetrance breast and prostate cancer genes. *Nat Rev Cancer*, 5, 977-85 (2005)
211. Bratt, O., A. Borg, U. Kristoffersson, R. Lundgren, Q. X. Zhang & H. Olsson: CAG repeat length in the androgen receptor gene is related to age at diagnosis of prostate cancer and response to endocrine therapy, but not to prostate cancer risk. *Br J Cancer*, 81, 672-6. (1999)
212. Krishnaswamy, V., T. Kumarasamy, V. Venkatesan, S. Shroff, V. R. Jayanth & S. F. Paul: South Indian men with reduced CAG repeat length in the androgen receptor gene have an increased risk of prostate cancer. *J Hum Genet* (2006)
213. Loukola, A., M. Chadha, S. G. Penn, D. Rank, D. V. Conti, D. Thompson, M. Cicek, B. Love, V. Bivolarevic, Q. Yang, Y. Jiang, D. K. Hanzel, K. Dains, P. L. Paris, G. Casey & J. S. Witte: Comprehensive evaluation of the association between prostate cancer and genotypes/haplotypes in CYP17A1, CYP3A4, and SRD5A2. *Eur J Hum Genet*, 12, 321-32. (2004)

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